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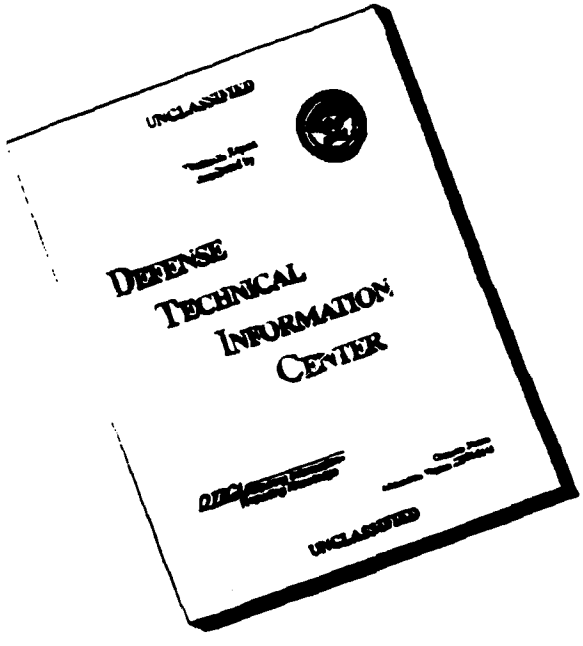

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CONTRACT NO.: DAMD17-90-C-0011

TITLE: SYNTHESIS OF POTENTIAL PROPHYLACTIC AGENTS AGAINST CYANIDE INTOXICATION.

PRINCIPAL INVESTIGATOR: James R. Piper

CONTRACTING ORGANIZATION: Southern Research Institute
2000 Ninth Avenue, South
P. O. Box 55305
Birmingham, Alabama 35255-5305

REPORT DATE: May 6, 1993

TYPE OF REPORT: Final Report

PREPARED FOR: U. A. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
FORT DETRICK
FREDERICK, MARYLAND 21702-5012

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13. ABSTRACT *(Maximum 200 words)*

The goal of the proposed research is to provide prophylaxis against cyanide through its sequestration by covalent bond formation. Three strategies were pursued: (1) sulfur-rich compounds which could serve as sulfane sulfur donors to rhodanese and other sulfur transferases; (2) compounds containing multiple carbonyl moieties, including analogs of pyruvate and α-ketoglutarate, which can bind cyanide through cyanohydrin formation; and (3) additional classes of compounds that can directly react with cyanide, such as (i) *N*-alkoxy and *N*-alkylthio heterocycles, and (ii) phthalocyanines and porphyrins. During this report period we prepared examples of all compound types just described. The 148 new compounds submitted this period were distributed among these compound classes as follows: sulfur-rich species, 55; polycarbonyl compounds, 39; nitrogenous heterocycles, 40; and metal complexes, 9. Some of these compounds contained multiple functionality that could react with cyanide. One of the sulfur compounds was prepared at the request of the CO and was a re-submission of an additional quantity of a previously submitted sample which had displayed positive biological results during screening (SoRI 7638; WR 268831). We have received biological testing data for 96 compounds during this same period, and now have demonstrated activity in three of our four primary target classes (no phthalocyanines have been tested for efficacy at this point). Of the screened compounds, five were found to have potential as an improved pretreatment for NaCN poisoning, with many additional possibilities as yet unscreened. These results were used to shape our planned synthetic program of our pending, renewal application.

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FOREWORD

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In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

PI – Signature James R. Piper DATE May 10, 1993

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I. INTRODUCTION

This report documents our efforts during the term of Contract No. DAMD17-90-C-0011 (9 March 1990 — 8 August 1993). The objective has been to identify new and improved prophylactic agents against the toxicity of cyanide. The synthetic effort has encompassed the areas described in this report, the detailed rationale for which is fully delineated in the original proposal (Southern Research Institute Proposal No. 88-483; USAMRDC Proposal Log No. 88321006): (i) polysulfides and other sulfur-rich compounds which can mediate cyanide detoxification through their interplay with rhodanese and other mammalian sulfur transferase systems; (ii) polycarbonyl-containing compounds which can provide multiple sites for cyanohydrin formation, one of the key detoxification routes of pyruvate and related compounds; (iii) heteroaromatic compounds capable of undergoing cyanation, thereby removing cyanide; and (iv) a novel class of promising prophylactic substances, metal complexes including phthalocyanines, porphyrins, and simple cobalt salts that can sequester cyanide through complexation with the constituent metal ion.

This report compiles the synthetic procedures performed under this contract. We have also colligated structures of all compounds supplied for testing with their corresponding identification numbers and, where available, biological test data. Experimental procedures outlining the syntheses are provided following each section.

The following instrumentation methods and procedures were used. All solvents and materials were reagent grade and were either used as received or purified as required. ^{1}H NMR and ^{13}C NMR spectra were run with a Nicolet NMC NT300 NB spectrometer operating at 300.65 MHz with tetramethylsilane as an internal reference. Chemical shifts (δ) for multiplets were measured from the appropriate centers. The mass spectral data were obtained from a Varian MAT 311A mass spectrometer in fast atom bombardment (FAB) or electron-impact (EI) mode (direct probe temperature 20 °C), as indicated. Infrared data were obtained with a Nicolet 10-MX spectrometer. In most cases, only strong or medium peaks in the 1800-600 cm^{-1} range were reported. UV absorption spectra were determined in the appropriate solutions [pH 1 (0.1 *N* HCl), pH 7 buffer, and pH 13 (0.1 *N* NaOH)] with either a Cary 17 spectrometer or a Perkin-Elmer Model Lambda 9 UV/VIS/NIR spectrophotometer. Melting point data was obtained with a Mel-Temp Capillary Melting Point apparatus, and all melting points are uncorrected. Elemental analysis data were obtained from either an in-

house Perkin Elmer Model 240 Elemental Analyzer or from Atlantic Microlab of Atlanta, Georgia.

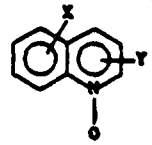
II. HETEROAROMATIC COMPOUNDS CAPABLE OF UNDERGOING CYANATION.

A. *N*-ALKOXY QUATERNARY SALTS AND RELATED COMPOUNDS DERIVED FROM *N*-OXIDES OF HETEROAROMATIC COMPOUNDS.

1. *N*-Alkoxy Quaternary Salts.

The capacity of *N*-alkoxy quaternary salts derived from heteroaromatic *N*-oxides to undergo cyanation in the ring was reported in 1959.[1-3] Numerous papers that describe the conversion and modifications have appeared in the three decades since. Reviews have been published,[4,5] and a recent publication affords an update.[6]

We initially prepared 11 target compounds of the *N*-alkoxy quaternary salt type by direct alkylations with halides or sulfates. Of these, there were six pyridine derivatives (structure numbers 14-19, Table 2A), four of the quinoline type (structure numbers 20, 22-24, Table 2B), and one derived from isoquinoline (21, Table 2B). As a result of the activity data for one of these initially submitted derivative (SoRI 7726, BM 07230), we prepared two additional *N*-alkoxy quaternary salts, 32 and 33. These compounds were prepared by standard procedures from the appropriate *N*-oxides 1-13 (structures shown below; analytical data summarized in Table 1). Of the *N*-oxides, three (1, 9, 10) were purchased from a commercial supplier, and we prepared the remainder from commercially available precursors.



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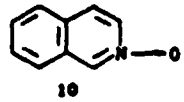

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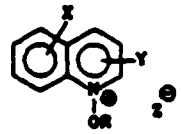
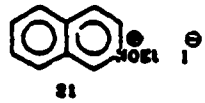
No.	Substituents	No.	Substituents
1	Unsubstd.	9	Unsubstd.
2	2,3-Me_2	11	6-Me
3	2,4-Me_2	12	4-Me
4	2,6-Me_2	13	4,7-Cl_2
5	2,6-Cl_2		
6	4-OMe		
7	2-OMe		





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No.	Substituents	R	Z	No.	Substituents	R	Z
14	2,3-Me_2	Et	I	20	Unsubstd.	Me	OSO_3H
15	2,4-Me_2	Et	I	22	6-Me	Et	I
16	2,6-Me_2	Et	I	23	4-Me	Et	Br
17	2,6-Cl_2	Me	OSO_3Me	24	4,7-Cl_2	Me	OSO_3Me
18	4-OMe	Et	I				
19	2-OMe	Me	OSO_3Me				

TABLE 1. HETEROAROMATIC *N*-OXIDES

Compd. No.	Substituents	Method	Yield, %	Mp, °C or Bp, °C/mm Hg) (lit. value)	Molec. Form.	Mass (FAB), *m/e*
Part A.	Substituted Pyridine *N*-oxides.					
2	2,3-Me_2	A	66	bp 16°/15 (lit[a] bp 118°/4)	C_7H_9NO	124
3	2,4-Me_2	A	75	bp 110°/1 (lit[b] bp 110°/1)	C_7H_9NO	124
4	2,6-Me_2	A	92	bp 120°/21 (lit[c] bp 120-123°/21)	C_7H_9NO	124
5	2,6-Cl_2	A[d]	72	mp 139° (lit[e] mp 139.5-140.5°)	$C_5H_3Cl_2NO$	163
6	4-OMe	A	45	mp 73-79° (lit[f] mp 73-74°)	$C_6H_7NO_2$	--
7	2-OMe	A	50	mp 66° (lit[f] mp 65-66°)	$C_6H_7NO_2$	126
Part B.	Pyrazine 1-oxide.					
8		A	33	mp 104° (lit[g] mp 104°)	$C_4H_4N_2O$	97
Part C.	Substituted Quinoline *N*-oxides.					
11	6-Me	B	74	mp 52-54° (lit[h] mp 52-54)	$C_{10}H_9NO$	159
12	4-Me	B	65	mp 112-115° (lit[h] mp 113-115°)	$C_{10}H_9NO$	159
13	4,7-Cl_2	B	84	mp 144° (lit[i] mp 165-167)[j]	$C_9H_5Cl_2NO$	214

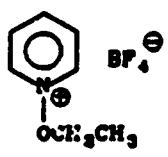
[a]Evans, R. F.; Kynaston, W. *J. Chem. Soc.* 1961, 5556. [b]Ruetgerswerke and Teerverwertung, *Chem. Abstr.* 1965, *62*, 9115d. [c]Chumakov, Yu, I., *Chem. Abstr.* 1964, *61*, 10652. [d]Trifluoroacetic acid and 30% H_2O_2 were used as reported in ref. e. [e]Rousseau, R. J.; Robins, R. K.. *J. Heterocycl. Chem.* 1965, *2*, 196. [f]Ochiai, E.; Teshigawara, T.; Oda, K.; Naito, T. *Chem. Abstr.*, 1960, *45*, 5153. [g]Klein, B.; Berkowitz, J. *J. Org. Chem.*, 1960, *8*, 5160. [h]Profft, E.; Buchmann, G.; Wackrow, N. *Arzneim.-Forsch.* 1960, *10*, 1029. [i]Elslager, E. F.; Grold, E. H.; Tendick, F. H.; Werbel, L. M.; Worth, D. F. *J. Heterocycl. Chem.*, 1964, *1*, 6. [j]Our sample of mp 144 °C gave the following elemental analysis results: *Anal.* Calcd for $C_9H_5Cl_2NO$: C, 50.50; H, 2.35; N, 6.54. Found: C, 50.54; H, 2.58; N, 6.19.

TABLE 2. *N*-ALKOXY QUATERNARY SALTS 14-24.

Compd. No.	Substituents, Reactants	Yield, %	Mp, °C	Molec. Form. (cation•anion)	Elemental Analyses Calcd / Found %C	%H	%N	Mass (pos. FAB), *m/e* cation. anion
Part A.	1-Alkoxypyridinium salts.							
14	2,3-Me_2, 2 + EtI	87	120-122	$C_9H_{14}INO$ ($C_9H_{14}NO$•I)	38.72 38.96	5.05 5.26	5.01 4.92	152, 126
15	2,4-Me_2, 3 + EtI	88	118-120	$C_9H_{14}INO$ ($C_9H_{14}NO$•I)	38.72 38.81	5.05 5.23	5.01 4.95	152 126
16	2,6-Me_2, 4 + EtI	88	88-90	$C_9H_{14}INO$ ($C_9H_{14}NO$•I)	38.72 38.19	5.05 5.02	5.01 4.97	152, 126
17	2,6-Cl_2, 5 + $(MeO)_2SO_2$	71	80	$C_7H_9Cl_2NO_5S$ ($C_6H_6Cl_2NO$•OSO_2OCH_3)	28.98 28.62	3.12 3.22	4.82 4.40	178, 111
18	4-OMe,6 + EtI	78	46-48	$C_8H_{12}INO_2$ ($C_8H_{12}NO_2$•I)	34.18 34.02	4.30 4.91	4.98 4.33	154, 126
19	2-OMe, 7 + $(MeO)_2SO_2$	76	oil	$C_8H_{13}NO_6S$ ($C_7H_{10}NO_2$•OSO_2OCH_3)	38.24 38.36	5.1[illegible] 5.1[illegible]	5.57 6.01	140, 111
Part B.	1-Alkoxyquinolinium salts.							
20[a]	Quinoline *N*-oxide, 9 + $(MeO)_2SO_2$	38	152-154	($C_{10}H_{11}NO_5S$ ($C_{10}H_{10}NO$•OSO_2OH)	46.68 46.40	4.31 4.31	5.44 5.38	160, 97
21	Isoquinoline *N*-oxide, 10 + EtI	68	136-138	$C_{11}H_{12}INO$ ($C_{11}H_{12}NO$•I)	43.37 43.57	4.01 4.08	4.65 4.61	174, 126
22	6-Me, 11 + EtI	42	82-84	$C_{12}H_{15}INO$ ($C_{12}H_{15}NO$•I)	45.68 45.42	4.78 4.25	4.43 4.39	188, 126
23	4-Me, 12 + EtBr	82	90	$C_{12}H_{14}BrNO$ ($C_{12}H_{14}NO$•Br)	53.75 53.78	5.26 5.56	5.22 5.33	188, 79
24	4,7-Cl_2, 13 + $(MeO)_2SO_2$	55	48-52	$C_{11}H_{11}Cl_2NO_5S$ ($C_{10}H_8Cl_2NO$•OSO_2OCH_3)	38.83 38.75	3.25 3.17	4.11 3.92	228, 111

[a]Prepared by the procedure of Takayama, H.; Okamoto, T. *Chem. Pharm. Bull.* 1978, *26*, 2435, but we obtained the hydrogen sulfate salt instead of the methyl sulfate salt as reported. This was evidenced by the elemental analysis results and mass spectral data listed above.

Pyrazine 1-oxide (8, Table 1) was also prepared. Although we could not alkylate 8 with alkyl iodides, we were able to prepare the *O*-ethyl tetrafluoroborate salt 26 by treatment of 8 with triethyloxonium tetrafluoroborate in chloroform. The procedure was adapted from a reported method[27] in which 9 was reported not to react with ethyl iodide to form the *O*-ethyl salt.[28] However, with triethyloxonium tetrafluoroborate, the *O*-ethyl derivatives 25-28 formed readily; they were isolated as tetrafluoroborate salts. Results are listed in Table 3.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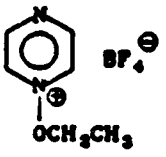
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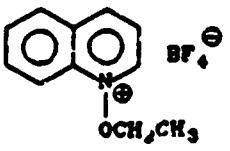
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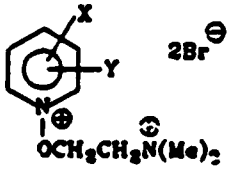
2. 1-[(2-Trimethylammonium)ethoxy]pyridinium Salts.

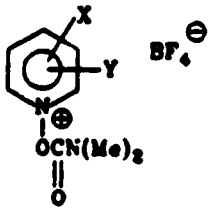
Five related compounds in which the *O*-substituent is the 2-(trimethylammonium)-ethyl group were also prepared; these are structure numbers 29-33 shown below. Results are listed in Table 4. These compounds were prepared by treating the appropriate *N*-oxide with (2-bromoethyl)trimethylammonium bromide as described in a reported procedure (see footnote, Table 4).



No.	Substituent
29	unsubstd.
30	2,4-Me
31	2,3-Me
32	2,6-Me
33	4-Me

3. 1-(*N,N*-Dimethylcarbamoyloxy)pyridinium Tetrafluoroborates.

The *N,N*-dialkylcarbamoyl derivatives 34 and 35 were prepared by adaptation of a reported method.[4] Results are summarized in Table 5.



No.	Substituent
34	unsubstd.
35	2,4-Me_2

TABLE 3. *N*-ETHOXY QUATERNARY SALTS 25-28 FORMED FROM TRIETHYLOXONIUM TETRAFLUOROBORATE AND *N*-OXIDES 1, 8, 9, AND 10.

Compd. No.	Reaction time, h	Yield, %	Mp °C	Molec. Form.	Elemental Analyses Calcd Found %C	%H	%N	Mass (pos. FAB) *m/e* cation, anion
25	24	88	viscous oil	$C_7H_{10}NO{\cdot}BF_4$	39.85 40.12	4.78 4.74	6.64 6.96	124,87
26	12	45	96-98	$C_6H_9N_2O{\cdot}BF_4$	34.00 34.00	4.28 4.24	13.22 13.34	125,87
27	0.25	98	82-84	$C_{11}H_{12}NO{\cdot}BF_4$	50.62 50.91	4.63 4.73	5.37 5.16	174,87
28	0.25	92	109-110	$C_{11}H_{12}NO{\cdot}BF_4$	50.62 50.31	4.63 4.78	5.37 5.13	174,87

TABLE 4. 1-[2-(TRIMETHYLAMMONIUM)ETHOXY]PYRIDINIUM SALTS.

Compd. No.	Substituents and reaction condns	Yield, %	Mp, °C	Molec. Form.	Elemental Analyses Calcd Found %C	%H	%N	Mass (pos. FAB), *m/e* cation
29	Pyridine *N*-oxide, 1 + $Br(CH_2)_2N(Me)_3^{\oplus}$ $Br^{\ominus}$	72	196-198 (lit.[a] 198)	$C_{10}H_{18}Br_2N_2O$	35.11 35.56	5.34 5.40	8.19 8.02	261
30	2,3-diMe, 2 + $Br(CH_2)_2N(Me)_3^{\oplus}$ $Br^{\ominus}$	65	195-199 (lit.[a] 195)	$C_{12}H_{22}Br_2N_2O$	38.94 38.62	5.99 6.20	7.56 7.60	289
31	2,4-diMe, 3 + $Br(CH_2)_2N(Me)_3^{\oplus}$ $Br^{\ominus}$ refluxing MeCN	66	164	$C_{12}H_{22}Br_2N_2O{\cdot}1.5H_2O$	36.29 36.50	6.34 6.10	7.05 7.28	289
32	2,6-diMe, 4 + $Br(CH_2)_2N(Me)_3^{\oplus}$ $Br^{\ominus}$	68	175 (lit.[a] mp 175-176)	$C_{12}H_{22}Bn_2N_2O{\cdot}H_2O$ (388.16)	37.13 37.14	6.23 6.29	7.22 7.15	289, 79
33	4-Me + $Br(CH_2)_2N(Me)_3^{\oplus}$ $Br^{\ominus}$	61	184-185 (lit.[a] mp 182-190)	$C_{11}H_{20}Bn_2N_2O$ (356.12)	37.10 36.96	5.66 5.42	7.87 7.76	275, 79

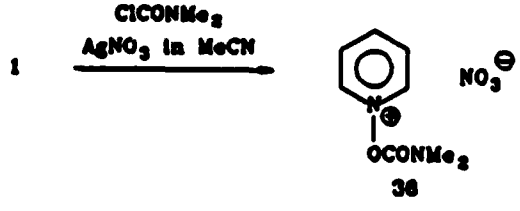
[a]Augustinsson, K. B.; Hasselquist, H. *Acta Chem. Scand.* 1961, *15*, 817.

TABLE 5. REACTIONS OF *N*-OXIDES 1, 3, AND 4 WITH *N,N*-DIALKYLCARBAMOYL CHLORIDES IN PRESENCE OF TETRAFLUOROBORIC ACID-DIETHYL ETHER COMPLEX.

Compd. No.	Reactant + R_2NCOCl (reaction time, h)	Yield, %	Mp, °C	Molec. Form. (cation•anion)	Elemental Analyses Calcd Found %C	%H	%N	Mass (FAB) cation, anion
34	1 + Me_2NCOCl (18 h)	72	oil	$C_8H_{11}BF_4N_2O_2•H_2O$ ($C_8H_{11}N_2O_2•BF_4$)	35.32 35.56	4.82 4.34	10.30 9.55	167, 87
35	3 + Me_2NCOCl (24)	50	88-90	$C_{10}H_{15}BF_4N_2O_2$ ($C_{10}H_{15}N_2O_2•BF_4$)	42.58 42.38	5.36 5.36	9.93 9.79	195, 87
[a]	1 + Et_2NCOCl (4 h)	48	64-65	$C_5H_6BF_4NO$[a] ($C_5H_6NO•BF_4$)	32.83 32.35	3.31 3.55	7.66 7.86	96, 87
[a]	4 + Me_2NCOCl (2 h)	40	110	$C_7H_{10}BF_4NO$[a] ($C_7H_{10}NO•BF_4$)	39.85 39.55	4.78 4.94	6.64 6.77	124, 87

[a]Expected product did not form; isolated material was the tetrafluoroborate salt of starting *N*-oxide.

The tetrafluoroborate salt 34 was an oil which resisted crystallization. In a later experiment, we reexamined treatment of 1 with *N,N*-dimethylcarbamoyl chloride in the presence of $AgNO_3$ (instead of $Et_2O•HBF_4$), and isolated the *O*-carbamoylated product as its crystalline nitrate salt 36 shown below.



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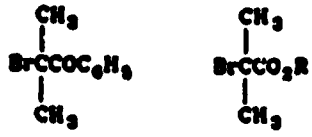
4. *N*-Alkoxy Quaternary Salts Prepared by Reaction of *N*-Oxides With α-Bromoisobutyrophenone and α-Bromoisobutyric Acid Esters.

Another series of *O*-alkylated candidates was suggested by the work of Sliwa and coworkers.[6,9] The Sliwa-type compounds are derived from α-bromoisobutyrophenone (37) and esters of α-bromoisobutyric acid (ethyl ester 38; *t*-butyl ester 39).



37

38: R = $-CH_2CH_3$
39: R = $-C(CH_3)_3$

The alkylation reactions using these commercially available bromo compounds and *N*-oxides 1, 4, and 5 were carried out in acetonitrile in the presence of $AgNO_3$. Thus the products were obtained as nitrate salts. Target compounds (structure numbers 40-47) prepared in this series are listed in Table 6.

EXPERIMENTAL SECTION FOR PART II. A.

Substituted Pyridine *N*-Oxides (2-7) Method A. (see Table 1A). These compounds were prepared by treatment of the appropriate starting compounds with 30% H_2O_2 according to the general procedure of Evans and Kynaston (see footnote a, Table 1A). One exception was compound 5 as noted in Table 1A. Their physical properties agreed with reported values, and mass spectral data agreed with that expected for the assigned structure.

Pyrazine 1-Oxide (8) was prepared according to a reported procedure as listed in Table 1B.

Substituted Quinoline *N*-Oxides (11-13) (Method B) (see Table 1C). A solution of equimolar amounts (0.100-mol each) of the appropriate substituted quinoline and *m*-chloroperbenzoic acid in $CHCl_3$ (125 mL) was refluxed 2-4 h. The cooled solution was washed with 10% Na_2CO_3 solution followed by H_2O, then dried (over anhydrous K_2CO_3), filtered, and evaporated. The residue was recrystallized twice from EtOH to give the results listed in Table 1C.

***N*-Alkoxypyridinium or quinolinium Salts (14-24) (see Table 2). A. Halide Salts (14-16, 18, 21-23).** The solution that formed when equimolar amounts (50 mmol each) of the alkyl halide and the appropriate *N*-oxide were mixed was kept in a stoppered flask at 20-23 °C for 20 h. The solutions usually turned a reddish color while changing to a crystalline mass. The crude product was stirred with EtOAc, collected, washed with Et_2O, and recrystallized from EtOH-Me_2CO. Final products were dried *in vacuo* (20-23 °C over P_2O_5) for 2-4 h. Results are listed in Table 2. **B. Sulfate Salts (17, 19, 20, 24).** Me_2SO_4 (0.150 mol) was gradually added to the appropriate *N*-oxide (0.100 mol), and the resulting mixture was heated in a 100 °C H_2O bath for 2-4 h or kept at 20-23 °C for 20-48 h. The reaction mixture (except for 20 described in note below), now consisting mostly of crystalline solid (except for 19), was stirred with Me_2CO, and the solid present was collected and washed with Et_2O. Recrystallization from MeOH-$CHCl_3$ followed. Products were dried *in vacuo* (over P_2O_5). Results are listed in Table 2. Compound 19, which did not crystallize, was stirred with Me_2CO and Et_2O, each of which was decanted away, and the oil was dried *in vacuo*. Note:

During workup of 20, the reaction mixture was dissolved in H_2O, and the solution was evaporated to dryness. The residue was recrystallized from MeOH-Me_2CO; elemental analysis and mass spectral results showed the product to be the hydrogen sulfate salt as indicated in Table 2 instead of the methyl sulfate salt.

N-Ethoxy Quaternary Tetrafluoroborates 25-28 (Table 3). Triethyloxonium tetrafluoro-borate (3.80 g, 0.020 mol; Lancaster Synthesis Ltd.) was added to a solution of the appropriate *N*-oxide (0.020 mol) in $CHCl_3$ (20 mL) kept at 0-5°C. Stirring in the cold was continued for the time listed in Table 3. With the exception of 25, the products separated from solution as crystalline solids. The solid was collected by filtration, washed with Et_2O, recrystallized from MeOH, and then dried *in vacuo* at 20-25 °C over P_2O_5. For isolation of 25, the solvent ($CHCl_3$) was evaporated under reduced pressure (H_2O pump, bath at 25 C), and the residual clear oil was washed with two or three portions of Et_2O, which were removed by decantation. The colorless oil was then dried *in vacuo* over P_2O_5 at 40 °C. Results are listed in Table 3.

N-[2-(Trimethylammonium)ethoxy]pyridinium Dibromides (29-33) (See Table 4). These compounds were prepared by direct *O*-alkylation of the appropriate pyridine *N*-oxide with (2-bromoethyl)trimethylammonium bromide according to reported procedures.[26] The mass spectrum (FAB positive) of these compounds revealed a bromine associated with the positive ion. Assigned structures were confirmed by ^1H NMR spectra. The following preparations for 32 and 33 are provided as examples.

Synthesis of *N*-[2-trimethylammonium)ethoxy]-2,6-dimethylpyridinium Dibromide (32).[26] A mixture of 2-bromoethyltrimethylammonium bromide (8.2 mmol), 2,6-lutidine-*N*-oxide (8.1 mmol), and 5 mL of water was heated in a flask at 100 °C for 56 h. The unreacted bromoethyl compound was removed by adding an additional portion of water (10 mL), followed by evaporation under reduced pressure. This process was repeated twice. The lutidine which was formed during the reaction was removed by extraction with chloroform. The remaining product was treated with ethanol, filtered, and the residue dissolved in boiling ethanol. The solution was treated with activated carbon, filtered, and the filtrate cooled to get the crystalline compound. The product was dried over P_2O_5 under reduced pressure. Yield 68%; mp 175 °C (Lit 175.5 °C). Anal. Calcd for $C_{12}H_{22}ON_2Br_2 \cdot H_2O$. C, 37.13; H, 6.23; N, 7.22. Found: C, 37.14; H, 6.29; N, 7.15. MS (FAB) *m/e* 289, cation, 79 anion.

Synthesis of *N*-[2-(trimethylammonium)ethoxy]4-methylpyridinium dibromide (33).[26] A mixture

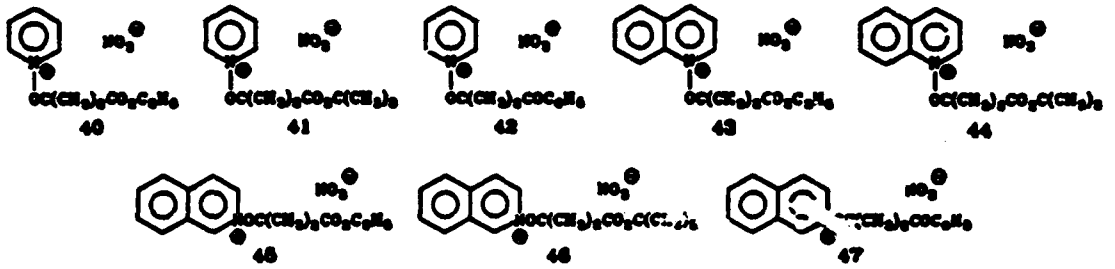
of 2-bromoethyltrimethylammonium bromide (14 mmol) and 4-methylpyridine-*N*-oxide (32 mmol) was refluxed in acetonitrile (10 mL) on a water bath for 10 h. The 2-bromoethyltrimethylammonium bromide slowly dissolved and a light brown solid separated, which was filtered and washed with acetonitrile (20 mL) and then acetone, and crystallized from *n*-butanol, followed by drying under reduced pressure. Yield 61%; mp 184-185 °C (lit 182-190 °C). Analysis for $C_{11}H_{20}ON_2Br_2$.

1-(*N,N*-Dimethylcarbamoyloxy)pyridinium Tetrafluoroborates (see Table 5). A solution of tetrafluoroboric acid - diethyl ether complex (40 mmol) in $CHCl_3$ (20 mL) was added dropwise to a stirred solution of *N,N*-dimethylcarbamoyl chloride (37.6 mmol) and substituted pyridine *N*-oxide (28.4 mmol) in $CHCl_3$ (40 mL) kept at 0-5 °C. The solution was allowed to warm and stirring was continued for 2 days longer. Products separated as solids or viscous oil. Washing by decantation with added portions of $CHCl_3$ followed. The $CHCl_3$-insoluble phase was finally washed with Et_2O, and the product was dried *in vacuo*. The expected products from two experiments did not form; only the tetrafluoroborate salts of the starting *N*-oxide were obtained from these attempts.

1-[(*N,N*-Dimethylcarbamoyl)oxy]pyridinium Nitrate (36). A solution *N,N*-dimethyl-carbamoyl chloride (5.35 g, 0.050 mol) in MeCN (20 mL) was added dropwise to a stirred solution of 1 (4.75 g, 0.050 mol) in MeCN (20 mL) with cooling by an ice-H_2O bath. A solution of $AgNO_3$ (8.1 g, 0.050 mol) was then added dropwise. The cooling bath was removed, and the mixture was stirred at 20-25 °C for 24 h. The precipitated AgCl was removed by filtration. The filtrate was evaporated (H_2O pump, bath at 25 °C), and the solid residue was collected with the aid of Et_2O. Finally, the solid was recrystallized from MeCN to give 36, mp 110-112 °C, in 86% yield. *Anal.* Calcd for $C_8H_{11}N_3O_5 \cdot H_2O$: C, 38.87; H, 5.30; N, 16.99. Found: C, 39.03, H, 4.62; N, 16.91. Spectral data: MS (FAB) *m/e* 167 cation, 62 anion in agreement with assigned structure.

***N*-Alkoxy Quaternary Salts 40-47 Prepared by Reaction of 1, 4, and 5 with α-Bromoisobutyrophenone (37) and α-Bromoisobutyric Acid Esters (38, Ethyl Ester; 39, *tert.*-Butyl Ester) (See Table 6).** A solution of the appropriate bromo compound 37, 38, or 39 (0.050 mol) in MeCN (20 mL) was added dropwise to a stirred solution of the appropriate *N*-oxide 1, 4, or 5 (0.050 mol) in MeCN (20 mL) with external cooling (ice-H_2O bath). A solution of $AgNO_3$ (0.050 mol) in MeCN (20 mL) was then also added

dropwise. The cooling bath was removed, and the mixture was stirred 24-72 h at 20-25 °C. The precipitate of AgBr was removed by filtration with the aid of MeCN. The clear filtrate was treated with Et_2O to cause precipitation of the reaction product. The nitrate salt was collected, washed with Et_2O, then recrystallized from MeOH. The collected and dried products gave the results listed in Table 6.

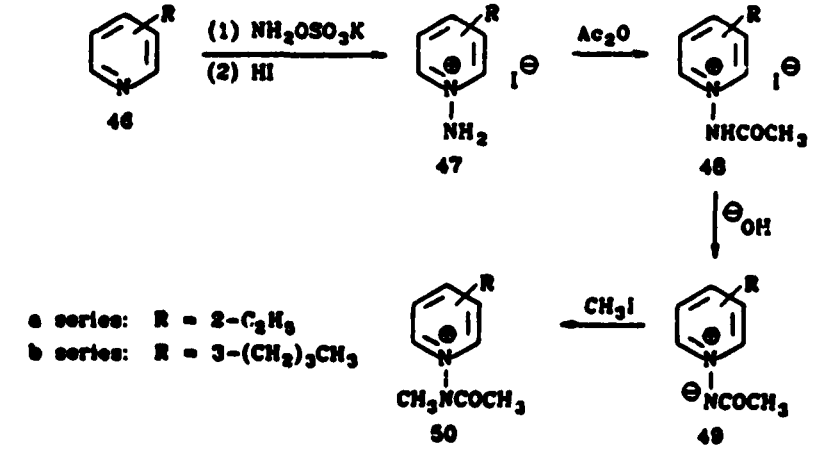


40 41 42 43 44 45 46 47

B. DERIVATIVES OF 1-AMINO QUATERNARY SALTS OF NITROGEN HETEROCYCLES.

1. 1-(*N*-Methylacetamido)alkylpyridinium Salts.

The facile cyanation of 1-(*N*-methylacetamido)alkylpyridium derivatives of structural type 50 (shown below) with cyanide ion as demonstrated by Okamoto *et al.*[10] prompted us to prepare representative examples as anticyanide candidates. The 2-ethyl compound 52a was prepared as described in the literature (work cited above), and the 3-butyl compound 52b was prepared in similar fashion. The synthesis is a four-step process. First, the appropriate alkylpyridine 48a or 48b is treated with potassium hydroxylamine-*O*-sulfonate (H_2NOSO_2K) in H_2O followed by HI to give the *N*-aminoalkylpyridinium iodides 49a,b. The iodide salts are then treated with acetic anhydride to give *N*-acetyl derivatives 50a,b. Treatment of iodide salts 50a,b in EtOH solution with basic ion exchange resin (Amberlite IRA-410) gave internal salt forms 1 (*N*-acetimido)alkylpyridines 51a,b. Alkylation with CH_3I then gave the target compounds 52a,b.



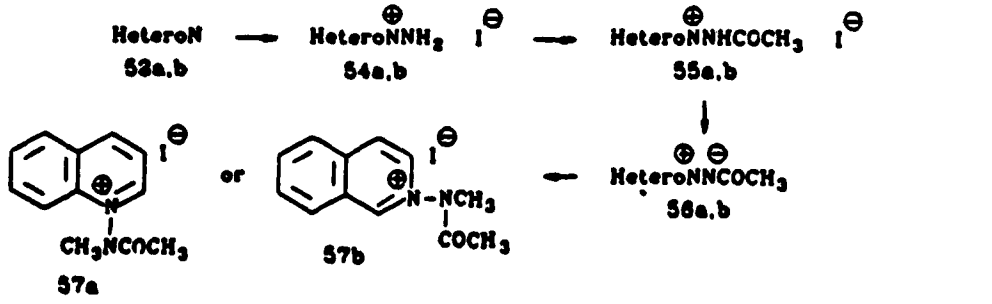
46 47 48 49 50

TABLE 6. *N*-ALKOXY QUATERNARY COMPOUNDS DERIVED FROM BROMO COMPOUNDS 12-14 AND *N*-OXIDES 1, 4, AND 5 IN MECN CONTAINING $AgNO_3$.

Compd. No.	Yield, %	Mp, °C	Molec. Form.	Elemental Analyses Calcd / Found %C	%H	%N	Mass (pos. FAB) *m/e* cation,anion
40	38	101	$C_{11}H_{16}NO_3 \cdot NO_3 \cdot 0.2H_2O$	47.89 47.92	5.98 5.93	10.16 10.21	210, 62
41	83	102-104	$C_{13}H_{20}NO_3 \cdot NO_3$	51.99 51.61	6.71 6.83	9.33 9.33	238, 62
42	91	124-125	$C_{15}H_{16}NO_2 \cdot NO_3$	59.21 59.36	5.30 5.44	9.21 9.26	242, 62
43	36	114-116	$C_{15}H_{18}NO_3 \cdot NO_3$	55.90 55.49	5.60 5.75	8.69 8.75	260, 62
44	42	84-86	$C_{17}H_{22}NO_3 \cdot NO_3 \cdot 0.5H_2O$	56.82 56.55	6.45 6.65	7.80 7.82	288, 62
45	81	76-78	$C_{15}H_{18}NO_3 \cdot NO_3$	55.90 55.59	5.60 5.74	8.69 8.65	260, 62
46	92	89-90	$C_{17}H_{22}NO_3 \cdot NO_3$	58.28 58.32	6.33 6.58	7.99 7.97	288, 62
47	86	124-125	$C_{19}H_{18}NO_2 \cdot NO_3$	64.40 64.24	5.12 5.31	7.91 8.10	292, 62

2. 1-(*N*-Methylacetamido)quinolinium Iodide and the Corresponding Isoquinolinium Iodide.

Title compounds **57a** and **57b** were prepared by essentially the same reaction sequence described above for pyridine analogues **52a,b**. The quinoline derivative **57a** was prepared as described in the literature by Okamoto *et al.*[10] using the general synthetic route outlined above for **52a,b**. The heretofore unreported isoquinoline analogue **57b** was similarly prepared.



a series: derived from quinoline
b series: derived from isoquinoline

EXPERIMENTAL SECTION FOR PART II.B.

1-Amino-2-ethylpyridinium Iodide (49a). Hydroxylamine-O-sulfonic acid (0.1 mol) in H_2O (20 mL) was neutralized with a solution of KOH (0.1 mol) in H_2O (20 mL). The resulting solution was added dropwise to a stirred solution of 2-ethylpyridine (48a, 0.1 mol) in H_2O (20 mL) maintained at 70 °C. Stirring at 70 °C was continued for 2 h. A solution of K_2CO_3 (0.1 mol) in H_2O (20 mL) was then added, and the solution was heated 45 min longer at 70 °C. The solution was then concentrated under reduced pressure (rotary evaporator, H_2O aspirator) to about 40 mL. Treatment with MeOH caused precipitation of inorganic salts, which were removed by filtration. The filtrate was treated with 57% HI in H_2O (12 mL), then chilled to -10 °C for 1 h, but the expected precipitation of 49a did not take place. The solution was evaporated to dryness under reduced pressure, and the residue was treated with four portions of EtOH (20-25 mL), each of which was evaporated off under reduced pressure to give 49a as a yellow solid, mp 108-110 °C (reported mp by Okamoto *et al.*[10] 107 °C): yield 22% (6.1 g).

1-(Acetamido)-2-ethylpyridinium Iodide (50a). A solution of 49a (6.0 g) in Ac_2O (45 mL) was kept at 95-100 °C (bath temperature) for 2 h. Evaporation under reduced pressure followed, and the residue was triturated with Et_2O. The Et_2O was decanted, and the residual oil was used without further workup in the next step.

1-(Acetimido)-2-ethylpyridine (51a). The oil described above (under 50a) was dissolved in EtOH (60 mL). This solution was passed through a column of anion exchange resin (Dowex 1 X 2-200) which had been pretreated with 1.5 *N* HCl, H_2O and then 10% NaOH in that order. The eluted EtOH solution was evaporated under reduced pressure to give crude 51a as a yellow oil. A solution of the oil in the minimum volume of EtOH was applied to a column of silica gel (3 x 25 cm, 230-400 mesh) poured from a slurry in $CHCl_3$-MeOH (95:5). Elution by $CHCl_3$-MeOH (95:5) followed. Fractions which gave a single spot on TLC were combined and evaporated to give 51a as a viscous red oil; yield 2.42 g (55% based on starting amount of 49a).

1-(*N*-Methylacetamido)-2-ethylpyridinium Iodide (52a). The sample of 51a described above (2.42 g) was dissolved in CH_3I (20 mL), and the solution was kept at 20-25 °C overnight. Evaporation of the CH_3I left a crystalline residue which was recrystallized from EtOH to give pure 52a as a light yellow solid, mp 128-

129 °C (Okamoto *et al.* describe 52a as a brown powder, mp 139 °C). *Anal.* Calcd for $C_{10}H_{15}N_2O \cdot I$: C, 39.23; H, 4.94; N, 9.15. Found: C, 39.33; H, 5.11; N, 9.22. Spectral data: MS (FAB) *m/z* 179 (cation), 127 (anion) in agreement with assigned structure.

1-Amino-3-butylpyridinium Iodide (50b), 1-(acetamido)-3-butylpyridinium Iodide (50b), and 1-(acetimido)-3-butylpyridinium Iodide (51b) were each prepared as described for the analogous 2-ethyl compounds (49a-51). The overall yield of 51b as a viscous liquid was 28%.

1-(*N*-Methylacetamido)-3-butylpyridinium Iodide (52b). Treatment of 51b with CH_3I gave 52b as a viscous red oil; yield 80% (based on starting amount of 51b). *Anal.* Calcd for $C_{12}H_{19}N_2O \cdot I \cdot H_2O$: C, 40.92; H, 6.01; N, 7.95. Found: C, 40.86; H, 5.49; N, 7.57. Spectral data: MS (FAB) *m/z* 207 cation, 127 (anion) in agreement with assigned structure.

1-Aminoquinolinium Iodide (54a). Treatment of quinoline (0.24 mol) with H_2NOSO_3K (0.12 mol) in H_2O at 70-80 °C with subsequent operations carried out as described by Okamoto *et al.* led to 54a, mp 175-178 °C dec, in 20% yield (lit. 10 mp 178-179 °C, 20% yield).

1-(Acetimido)quinolinium Iodide (56a). A solution of 54a (16.7 mmol) in Ac_2O (90 mL) was kept overnight at 20-25 °C. The solution was then mixed with H_2O (90 mL), and the mixture was chilled while it was made alkaline by treatment with 30% NaOH solution. The resulting mixture was extracted with $CHCl_3$ (200 mL). Evaporation of the dried (Na_2SO_4) and filtered solution gave 56a, mp 90-91° (lit.[10] mp 89-90 °C) in 58% yield.

1-(*N*-Methylacetamido)quinolinium (57a). Treatment of 56a (6.0 mmol) with CH_3I (14 mL) overnight at 20-25 °C was followed by evaporation under reduced pressure, and the residue was recrystallized from EtOH to give 57a, mp 170-172 °C dec (lit. mp 172-174 °C dec) in 62% yield. *Anal.* Calcd for $C_{12}H_{13}N_2O \cdot I$: C, 43.92; H, 3.99; N, 8.57. Found: C, 43.65; H, 4.24; N, 8.47. Spectral data: MS (FAB) *m/z* 201 (cation), 127 (anion) in agreement with assigned structure.

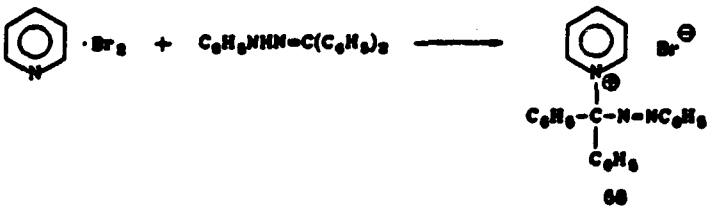
1-Aminoisoquinolinium Iodide (54b) was prepared from isoquinoline in the manner described for the preparation of 54a. The yield of 54b, mp 170-171 °C dec, was 20%. *Anal.* Calcd for $C_9H_9N_2 \cdot I$: C, 39.73; H, 3.33; N, 10.30. Found: C, 39.97; H, 3.52; N, 10.33. Spectra data: MS (FAB) *m/z* 145 (cation), 127 (anion) as expected.

1-(Acetimido)isoquinoline (56b) was prepared from 54b as described for conversion of 54a to 56a. The yield of 56b, mp 90-91 °C, was 62%.

1-(*N*-Methylacetamido) isoquinolinium Iodide (57b) was prepared by treatment of 56b with CH_3I as described for the conversion of 56a to 57a. The yield of 57b, mp 152-154 °C dec, was 76%. *Anal.* Calcd for $C_{12}H_{13}N_2O$-I: C, 43.92; H, 3.99; N, 8.57. Found: C, 44.16; H, 4.18; N, 8.45. Spectral data: MS (FAB) *m/z* 201 (cation), 127 (anion) as expected.

C. 1-(PHENYLAZODIPHENYLMETHYL)PYRIDINIUM BROMIDE.

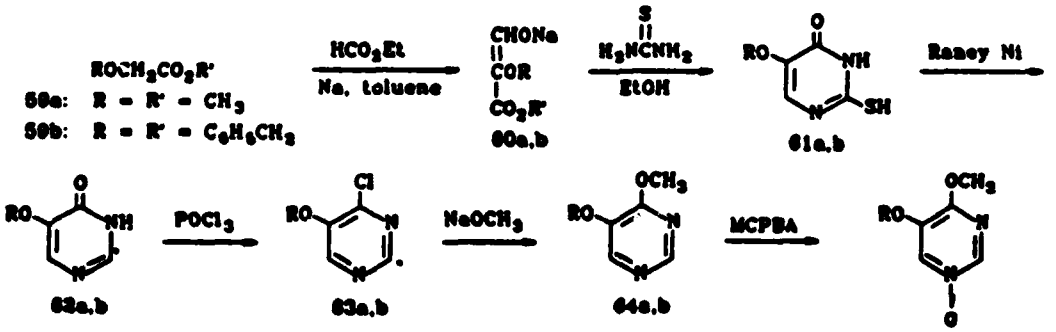
The title compound 58 (structure shown below) has been used in a reported synthesis of 4-cyanopyridine. Compound 58 reacts readily with KCN to form 4-cyanopyridine in 75% yield after purification. This demonstrated capacity to undergo cyanation indicates 58 to be a potential anticyanide agent. The reported multistep synthesis of 58 was used without modification to prepare a sample for anticyanide testing.



58

D. 4,5-DIALKOXYPYRIMIDINE *N*-OXIDES.

Screening candidate 4,5-dimethoxypyrimidine 1-oxide (65a) was a previously reported compound of demonstrated capacity to undergo cyanation.[11] Both the 4,5-dimethoxy compound 65a and an unreported analogue, 4-methoxy-5-(benzyloxy)pyrimidine 1-oxide (65b) were prepared for screening by the general route which follows. The intermediate 5-methoxy-4(3*H*)-pyrimidinone (62a) was prepared as indicated



following the procedure of Chesterfield *et al.*[12] The remaining three steps shown from 62a to target compound 65a were carried out as described by Yamanaka *et al.*[11] (In the literature report the chloro intermediate 63a is not isolated.)

Synthesis of the 4-methoxy-5-benzyloxy analogue 65b was achieved in similar fashion. The starting benzyloxyacetate ester was prepared by treatment of ethyl chloroacetate with sodium benzoxide in excess benzyl alcohol. Transesterification accompanied the displacement of chloride to give benzyl benzyloxyacetate (59b). Conversion of 59b to 5-benzyloxy-4(3*H*)-pyrimidinone (62b) was carried out as outlined using the procedures given by Chesterfield *et al.*[12] cited above. The remaining steps, formation of chloro compound 63b, displacement of chloro by methoxide and *N*-oxidation by MCPBA, were done in the manner reported for the 4,5-dimethoxy analogue.

EXPERIMENTAL SECTION FOR PART II.D.

2-Mercapto-5-methoxy-4(3*H*)-pyrimidinone (61a) was prepared as reported in the literature by the Na-promoted condensation of ethyl formate with methyl methoxyacetate to give the sodio derivative 60a which was condensed with thiourea to give 61a; yield 52%, mp 280-282 °C dec (reported[12] mp 280-281 °C dec).

5-Methoxy-4(3*H*)-pyrimidinone (62a). Treatment of 61a with Raney Ni in dilute NH_4OH solution as described in the literature gave 62a, mp 210-211 °C dec (in agreement with that reported[12]); yield 70%.

4,5-Dimethoxypyrimidine (64a). Conversion of 62a to 4-chloro-5-methoxypyrimidine (63a) by treatment with $POCl_3$ was followed by displacement of the chloro by methoxide as described by Yamanaka *et al.*[11] to give 64a in 68% yield; mp 74-76 °C (lit.[11] mp 76-77 °C).

4,5-Dimethoxypyrimidine 1-Oxide (65a). A solution of 64a (30 mmol) and *m*-chloroperbenzoic acid (50 mmol) in $CHCl_3$ (40 mL) was kept at 20-25 °C overnight (about 18 h). The mixture was washed with 20% K_2CO_3 solution and the $CHCl_3$ was removed by evaporation. The product was ultimately purified by column chromatography on 50-200 mesh silica gel with elution by $CHCl_3$-MeOH (95:5) to give pure 65a as a white solid, mp 209-210 °C dec (lit. mp 203-205 °C dec), in 51% yield. *Anal.* Calcd for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.17; H, 5.51; N, 17.82. Spectral data: MS (FAB) *m/z* 157, (MH^+).

5-Benzyloxy-4(3*H*)-pyrimidinone (62b). The synthesis began with treatment of ethyl chloroacetate

with the solution obtained by dissolving Na in benzyl alcohol exactly as described by Chesterfield *et al.*[12] to give benzyl benzyloxyacetate (59b), which was purified as reported by fractional distillation *in vacuo*. The outlined sequence was followed exactly as described by Chesterfield *et al.*[12] Each intermediate (61b and 62b) was purified as reported.

5-Benzyloxy-4-methoxypyrimidine 1-oxide (65b). The procedures used were like those used to convert 62a to 55a. Intermediate 62b was treated with $POCl_3$ to give the 4-chloro intermediate 63b, which was not purified but was treated immediately with $NaOCH_3$ in CH_3OH to give 64b. Oxidation by *m*-chloroperbenzoic acid followed to give 65b, mp 166-168 °C dec, in 45% overall yield (from 62b). *Anal.* Calcd for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 61.78; H, 5.23; N, 11.72. Spectral data: MS (FAB) 233 (MH^+).

E. *N*-ALKYL QUATERNARY SALTS.

Five substituted *N*-alkyl quaternary heterocyclic salts are depicted below (66-70). These compounds were prepared because of literature reports that pyridinium salts with glycosyl substituents at the 1-position and electron withdrawing groups at the 3-position react rapidly to form stable cyano adducts.[22,23] Glycosyl bromides were prepared by reported procedures,[24] then coupled with the parent heterocyclic compound. The results and physical properties of these agents are presented in Table 7.

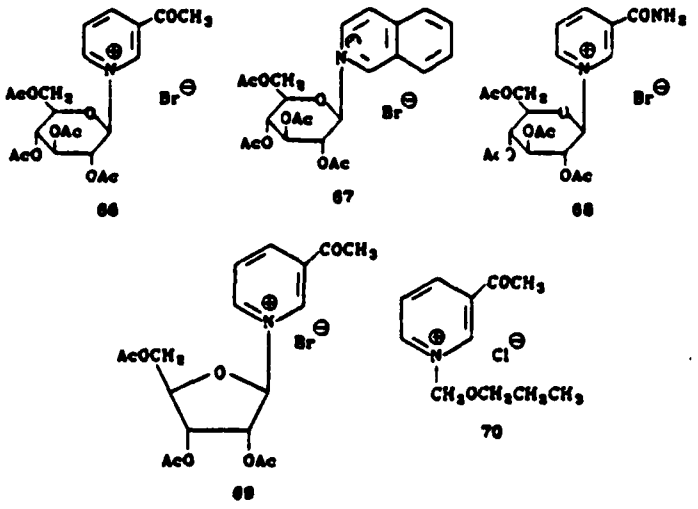


TABLE 7. QUATERNARY NITROGENOUS HETEROCYCLES.

Structure No.	Yield, %	Mp, °C	Molec. Form. (Formula Wt.)	Elemental Analyses Calcd / Found %C	%H	%N	Mass (FAB) cation, anion
66	39	158-159 (lit.[a] mp 158-159)	$C_{21}H_{26}BrNO_{10}$ (532.35)	47.38 47.57	4.92 5.00	2.66 2.66	452, 79
67	63	182-184	$C_{23}H_{26}BrNO_9$ (540.37)	51.12 50.90	4.85 5.02	2.59 2.61	460, 79
68	68	195-200 (lit.[b] mp 195-200)	$C_{20}H_{25}BrN_2O_{10}$ (533.34)	45.10 45.00	4.72 4.73	5.25 5.16	453, 79
69	52	58-60	$C_{18}H_{22}BrNO_8$ (460.28)	46.97 46.94	4.87 4.98	3.04 3.24	380, 79
70	60	142 (lit.[c] mp 142-143)	$C_{10}H_{15}ClN_2O_2$ (230.70)	52.06 51.74	6.55 6.50	12.14 12.09	195, 35

[a]Lovesey, A. C., *J. Med. Chem.* 1970, *13*, 693. [b]Haynes, L. J.; Todd, A. R., *J. Chem. Soc.* 1950, 303. [c]Lovesey, A. C.; Ross, W. C. J., *J. Chem. Soc. (B)* 1969, 192.

Acetobromo-D-glucopyranose used to prepare 66-68 and acetobromo-D-ribofuranose used to prepare 69 were prepared by the procedure of Haynes and Todd without modification.[24]. Chloromethyl propyl ether used to prepare 70 was prepared by the procedure of Henze *et al.*[27]

1,3-Disubstituted pyridinium halides 66, 68-70 and the isoquinolinium bromide 67 were prepared by treating the parent heterocyclic compound with the appropriate bromide or with chloromethyl propyl ether in refluxing acetonitrile using the general procedure of Lovesey.[23,24] Products crystallized from the reaction solutions. Names of the compounds are as follows: 3-acetyl-1-(2,3,4,6-tetraacetyl-β-D-glucopyranosyl)-pyridinium bromide (66); 1-(2,3,4,6-tetraacetyl-β-D-glucopyranosyl)isoquinolinium bromide (67); 3-aminocarbonyl-1-(2,3,4,6-tetraacetyl-D-glucopyranosyl)-pyridiniumbromide (68); 3-acetyl-1-(2,3,5-triacetyl-β-D-ribofuranosyl)pyridinium bromide (69); and 3-aminocarbonyl-1-(propoxymethyl)pyridinium chloride (70).

III. NITROGENOUS AROMATIC HETEROCYCLES.

Only a single example of this compound class was submitted for biological evaluation this report period, and the physical properties of this agent (71) are presented in Table 8. Our rationale for the

preparation and testing of this class of compounds was based upon the recent literature report[51] of the reaction of *N*-vinylpyrazolium salts with cyanide ion *in vitro*, and our desire to establish the potential utility of these compounds with regard to cyanide toxicity *in vivo*. The synthesis of this compound followed the preparation in the literature, and is shown below.

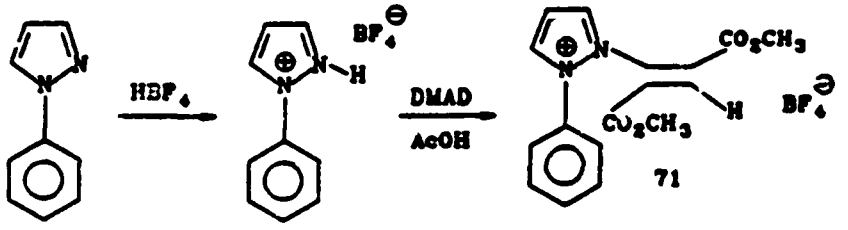


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TABLE 8. NITROGENOUS HETEROCYCLES

Structure No.	Yield, %	Mp, °C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd Found		
				%C	%H	%N
71	33	135-136	$C_{15}H_{15}N_2O_4BF_4$ (374.10)	48.16 48.06	4.04 3.96	7.49 7.41

EXPERIMENTAL SECTION FOR PART III.F.

Synthesis of 1-Phenyl-2-(1,2-dicarbomethoxy)vinylpyrazolium Tetrafluoroborate.

1-Phenyl-2-(1,2-dicarbomethoxy)vinylpyrazolium Tetrafluoroborate (71).

SoRI 8605.

Step 1. A solution of 3[illegible] mmole of pyrazole in 40 mL of ethanol was added with stirring to 3.74 g of 48% tetrafluoroboric acid. Stirring was continued for 1 h and then solvent was evaporated under reduced pressure, yielding a viscous, oily residue. Five mL of ethyl acetate was added and the oil then allowed to cool for 2 h at 0 °C. A white solid product crystallized, which was dried under reduced pressure to obtain the pure material, mp 95 °C. Yield 65%.

Step 2. Equimolar portions of 1-phenylpyrazolium tetrafluoroborate (3.4 g) and dimethylacetylene dicarboxylate (2.08 g) were dissolved in acetic acid (20 mL) and refluxed for 4 h. Solvent was removed under

reduced pressure. A yellow-orange, viscous liquid was obtained, to which ethyl acetate (5-10 mL) was added. Upon cooling (0 °C) the product crystallized. The solid was filtered, washed with ethyl acetate, and dried under reduced pressure to obtain the pure compound. Yield 51%, mp 135-135 °C. *Anal.* Calcd for $C_{16}H_{16}O_4N_2BF_4$: C, 48.15; H, 4.04; N, 7.49. Found: C, 48.06; H, 3.96; N, 7.41. MS (FAB) 287 $(M + 1)^+$, 285 $(M - 1)^-$.

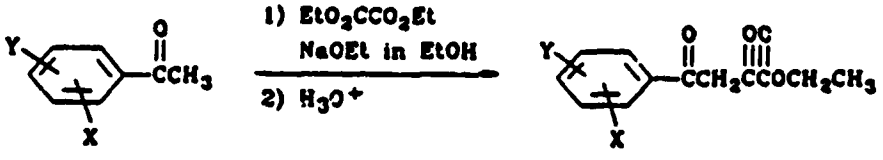
IV. POLYCARBONYL COMPOUNDS

A. DERIVATIVES OF 4-PHENYL-2,4-DIOXOBUTYRIC ACID.

Our rationale for preparing carbonyl compounds as potential cyanide ion traps *via* cyanohydrin formation was supported by a recent paper on protection against cyanide toxicity by α-ketoglutaric acid.[14]

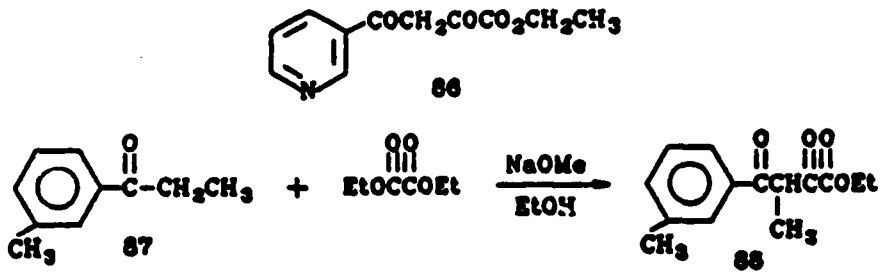
One series of polycarbonyl compounds was derived from acetophenone and variously substituted acetophenones by condensation with diethyl oxalate.[15,16] A number of the candidates prepared had already been reported in the literature, although not in connection with anticyanide studies.

The series prepared as ethyl esters is shown below.

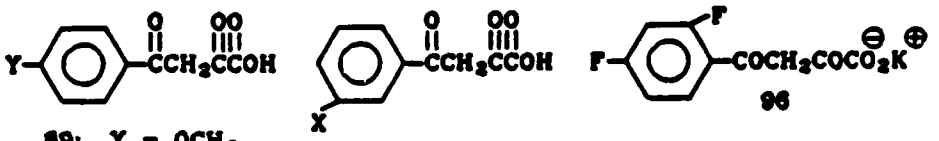


Compd. No.	X	Y
72	H	H
73	H	4-Cl
74	H	4-NO_2
75	2,4-F_2	
76	H	4-F
77	2,4-$(OCH_3)_2$	
78	H	4-OCH_3
79	3-CF_3	H
80	2,5-$(COCH_2COCO_2CH_2CH_3)_2$	
81	3-F	H
82	3-MeO	H
83	3-Cl	H
84	3-NO	H
85	3-Me	H

Similarly, pyridyl analogue **86** was prepared from 3-acetylpyridine, while ester **88** was prepared from propiophenone (**87**) as shown in the following scheme.



Eight of the esters were converted to the corresponding carboxylic acids (**88-96**) through hydrolysis while a ninth product precipitated as potassium salt **96** during the hydrolysis of **75**. The properites for acids **89-95** are provided in the Experimental Section.



EXPERIMENTAL SECTION FOR PART IV.

General Procedure for the Preparation of the 4-Phenyl-2,4-dioxobutyrate Esters 72-80.

Compounds **72-80** were prepared by the following general procedure.

Freshly cut Na (2.4 g, 0.105 mol) was added to EtOH (125 mL) under N_2 in a 500-mL, 3-neck flask equipped with a mechanical stirrer, a ground glass stopper, and a gas inlet tube. The mixture was stirred until the Na had completely dissolved, then equimolar amounts (0.100 mol each) of diethyl oxalate and the appropriate acetophenone) were added. (Different molar quantities were used in the preparation of **80**; see Experimental Section.) The reaction mixture was stirred for about 3 h, resulting in the formation of a thick slurry. If the thickness of the slurry interfered with stirring, more EtOH was added. Isolation of these compounds was achieved by one of the following methods:

(1) The slurry was filtered, and the collected solid was washed with anhydrous Et_2O until the wash solvent was colorless and the solid relatively dry. The solid was then added to H_2O, and the resulting partial

solution was acidified to pH 5 by the dropwise addition of glacial AcOH with stirring. The resulting solid was collected and dried *in vacuo*. When required, the compounds were further purified by reprecipitating them from solution in dilute NaOH by treatment with glacial AcOH to pH 3 followed by drying as before.

(2) The following isolation method was used if acidification of the solution of the Na salt of the product did not result in the formation of a precipitate (*e.g.*, Compound 72). The solid was collected, washed with Et_2O, suction dried for a time, then dissolved in H_2O. The resulting solution was acidified to pH 5 by the dropwise addition of glacial AcOH with stirring. The solution was then extracted with Et_2O and the Et_2O solution was evaporated until crystallization occurred. The resulting crystals were collected and dried *in vacuo* giving the desired product as off-white or light-yellow solids. Analytical data for these compounds is given below. The ^1H NMR spectra of these compounds in Me_2SO-d_6 indicated each to be largely in enol form.

Ethyl 4-Phenyl-2,4-dioxobutyrate (72). Yield 40%; mp 34-35 °C; MS (FAB) *m/e* 221 (M + 1); IR (KBr) 3045 (w), 3012 (w), 2990 (w), 1728, 1618.9, 1597.5, 1569.8, 1473.5, 1336.2, 1321.3, 1279.8, 1278.0, 1241.1, 1184.1, 1099.8, 1018.4, 768.3, 705.9 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.08 (d, 2, H-2'), 7.72 (m, 1, H4'), 7.58 (m, 2, H-3'), 7.12 (br s, 1, H-3), 4.32 (q, 2, $-OCH_2CH_3$), 1.32 (t, 3, $-OCH_2CH_3$), also very weak multiplets at 7.98, 4.23, and 1.24 for the keto tautomer. *Anal.* Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.48; H, 5.67. This compound was previously reported[16] to have mp 46 °C.

Ethyl 4-(4-Chlorophenyl)-2,4-dioxobutyrate (73). Yield 99%; mp 58-60 °C; MS (FAB) *m/e* 255 (M + 1); IR (Kbr) 3117 (w), 2988 (w), 2945 (w), 1730.1, 1719.9, 1590.8, 1480.8, 1367.3, 1299.8, 1279.4, 1270, 1176.6, 1108.2, 1090.5, 1009, 779.3, 767.2 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.08 (d, 2, H-3'), 7.64 (d, 2, H-2'), 7.09 (s, 1, H-3), 4.32 (q, 2, $-OCH_2CH_3$), 1.32 (t, 3, $-OCH_2CH_3$), very weak multiplets at 7.98, 4.23, 1.25 for the keto tautomer. *Anal.* Calcd for $C_{12}H_{11}ClO_4$: C, 56.69; H, 4.37. Found: C, 56.41; H, 4.35. Compound 73 was previously reported[15] to have mp 68-70 °C.

Ethyl 4-(4-Nitrophenyl)-2,4-dioxobutyrate (74). Yield 75%; mp 110-113 °C; MS (FAB) *m/e* 265 (M + 1); IR (KBr) 3120 (w), 2985 (w), 2940 (w), 1720.8, 1630.7, 1603.2, 1570, 1518.8, 1348.2, 1320.5, 1305.1, 1270.5, 1218.7, 111.2, 1106.7, 872.35, 759.3 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.32 (q, 4, Ph-H's), 7.13 (s, 1, H-3), 4.33 (q, 2, $-OCH_2CH_3$), 1.33 (t, 3, $-OCH_2CH_3$), very weak multiplets at 8.21, 4.23, 1.25 for the keto tautomer. *Anal.* Calcd for $C_{12}H_{11}NO_6$: C, 54.34; H, 4.15; N, 5.28. Found: C, 54.22; H, 4.34; N, 5.42. Compound 74

was previously reported[17] to have mp 116-117 °C.

Ethyl 4-(2,4-Difluorophenyl)-2,4-dioxobutyrate (75). Yield 99%; mp 102-104 °C; MS (FAB) *m/e* 256 (M + 1); IR (KBr) 3112 (w), 3085 (w), 2997 (w), 1725.9, 1604.5, 1491.1, 1369.2, 1280.1, 1264.1, 1236.6, 11436, 1100.4, 972.1, 879.7, 931.6, 781.1 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.0 (m, 1, H-6'), 7.48 (m, 1, H-3'), 7.30 (m, 1, H-5'), 6.87 (s, 1, H-3), 4.31 (q, 2, $-OCH_2CH_3$), 1.3 (t, 3, $-OCH_2CH_3$), also very weak multiplets at 7.95, 4.24, 1.26 for the keto tautomer. *Anal.* Calcd for $C_{12}H_{10}F_2O_4$: C, 56.03; H, 4.28. Found: C, 56.15; H, 4.04.

Ethyl 4-(4-Fluorophenyl-2,4-dioxobutyrate (76). Yield 99%; mp 41-43°C; MS (FAB) *m/e* 238 (M + 1); IR (KBr) 3055 (w), 2990 (w), 2905 (w), 1728.3, 1626.4, 1597.8, 1301.7, 1277.7, 1266.3, 1231.1, 1158.0, 856.9, 775.8, 591.0 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 15.23 (s, 1, H-3), 8.02 (q, 2, H-2'), 7.19 (t, 2, H-3'), 7.04 (s, 1, H-3), 4.41 (q, 2, $-OCH_2CH_3$), 1.42 (t, 3, OCH_2CH_3), also very weak multiplets at 1.25 for the unenolized tautomer. *Anal.* Calcd for $C_{12}H_{11}FO_4$: C, 60.50; H, 4.66. Found: C, 60.12; H, 4.73.

Ethyl 4-(2,4-Dimethoxyphenyl)-2,4-dioxobutyrate (77). Yield 43%; mp 78-81 °C; MS (FAB) *m/e* 280 (M + 1); IR (KBr) 3170 (w), 2960 (w), 2845 (w), 1607.1, 1598.2, 1576.3, 1269.7, 1240.7, 1216.4, 1175.9, 1112.8, 1018.2, 879.8 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.96 (d, 1, H-2'), 7.32 (s, 1, H-3), 6.58 (s, 1, H-3'), 6.47 (d, 1, H-5'), 4.38 (q, 2, $-OCH_2CH_3$), 3.93 (s, 3, CH_3O-4'), 3.87 (s, 3, CH_3O-2'), 1.32 (t, 3, $-OCH_2CH_3$), very weak multiplets at 4.15, 3.47, 1.3 for the unenolized tautomer. *Anal.* Calcd for $C_{14}H_{16}O_6 \cdot 0.33H_2O$: C, 58.74; H, 6.23. Found: C, 5[illegible] 99; H, 5.97.

Ethyl 4-(4-Methoxyphenyl)-2,4-dioxobutyrate (78). Yield 48%; mp 44-46 °C; MS (FAB) *m/e* 250 (M + 1); IR (KBr) 3005 (w), 2985 (w), 2945 (w), 1720.9, 1600.8, 1311.1, 1263.6, 1169.0, 1108.8, 1023.4, 773.44, 585.9 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.08 (d, 2, H-3'), 7.13 (s, 2, H-2'), 7.09 (s, 1, H-3), 4.32 (q, 2, $-OCH_2CH_3$), 3.88 (s, 3, $-OCH_3$), 1.32 (t, 3 $-OCH_2CH_3$), very weak multiplets at 7.96, 4.54, 4.23, 1.32 for the unenolized tautomer. *Anal.* Calcd for $C_{13}H_{14}O_5$: C, 62.40; H, 5.60. Found: C, 62.26; H, 5.76.

Ethyl 4-(3-Trifluoromethylphenyl)-2,4-dioxobutyrate (79) was prepared from 3-(trifluoromethyl)acetophenone as described in the general procedure. Pure 79, yield 29%; mp 32-35 °C, gave the following characterization data. *Anal.* Calcd for $C_{13}H_{11}F_3O_4$: C, 54.17; H, 3.85. Found: C, 54.12; H, 4.12. Spectral data: mass (FAB) *m/e* 289 (MH^+); ^1H NMR (Me_2SO-d_6) δ 8.39 (d, 1, H-4'), 8.32

(s, 1, H-2'), 8.09 (d, 1, H-6'), 7.82 (t, 1, H-5'), 7.20 (s, 2, H-3), 4.42 (q, 2, -OCH_2CH$_3$), 1.32 (t, 3, -OCH$_2$CH_3), also very weak multiplets at 4.23, 1.24 for the unenolized tautomer.

Triethyl α,α',α'',γ,γ',γ''-Hexaoxo-1,3,5-benzenetributanoate (80) was prepared by adaptation of the general procedure from 1,3,5-triacetylbenzene and three molar equivalents of diethyl oxalate using three molar equivalents of sodium ethoxide. Pure **80** was obtained as a monohydrate, yield 25%; mp 115 °C dec, and gave the following characterization data. *Anal.* Calcd for $C_{24}H_{24}O_{12}\cdot H_2O$: C, 55.17; H, 4.98. Found: C, 54.97; H, 4.83. Spectral data: mass (FAB) *m/e* 522 (MH^+); ^{1}H NMR (Me_2SO-d_6) δ 8.58 (s, 3, H-2'), 6.80 (s, 3, H-3), 4.27 (q, 6, -OCH_2CH$_3$), 1.31 (t, 9, -OCH$_2$CH_3), also very weak multiplets at 4.40, 4.07, 1.50, 1.19 for the unenolized tautomer.

Ethyl 4-(3-Fluorophenyl)-2,4-dioxobutyrate (81). Mp 56-57 °C; MS (FAB) *m/e* 239 (M + 1); IR (KBr) 3098.8, 2995.6, 1742.8, 1621.4, 1609.3, 1579.4, 1447.6, 1269.3, 1255.4, 1181.6, 1137.4, 1024.1, 774.3 cm^{-1}; ^{1} HNMR (Me_2SO-d_6) δ 14.60 (br s, 1, H-4), 7.94 (d, 1, H-6'), 7.87 (d, 1, H-5'), 7.63 (m, 1, H-2'), 7.58 (m, 1, H-4'), 7.13 (s, 1, H-3), 4.32 (q, 2, -OCH_2CH_3), 1.33 (t, 3, -OCH$_2$CH_3), also very weak multiplets at 4.61, 4.21, 1.26 for the unenolized tautomer. *Anal.* Calcd for $C_{12}H_{11}O_4$: C, 60.50; H, 4.62. Found: C, 60.56; H, 4.69.

Ethyl 4-(3-Methoxyphenyl)-2,4-dioxobutyrate (82). Mp 53-54 °C; MS (FAB) m/e 251 (M + 1); IR (KBr) 3132.4, 3089.9, 3000.0, 2845.6, 1742.4, 1595.6, 1580.0, 1470.0, 1185.2, 1135.6, 1021.4, 772.9, cm^{-1}; ^{1} HNMR (Me_2SO-d_6) δ 14.70 (br s, 1, H-4), 7.65 (d, 1, H-6'), 7.51 (s, 1, H-2'), 7.48 (d, 1, H-5'), 7.27 (m, 1, H-4'), 7.08 (br s, 1, H-3), 4.32 (q, 2, -OCH_2CH$_3$), 3.85 (s, 3, -OCH$_3$), 1.33 (t, 3, -OCH$_2$CH_3), also very weak multiplet at 4.60 for the unenolized tautomer. *Anal.* Calcd for $C_{13}H_{14}O_5$: C, 62.40; H, 5.60. Found: C, 62.34; H, 5.78.

Ethyl 4-(3-Chlorophenyl)-2,4-dioxobutyrate (83). Mp 55-57 °C; MS (FAB) m/e 255 (M+1); IR (KBr) 3120.9, 3100.0, 3016.6, 2999.8, 2950.1, 2917.6, 1975.0, 1732.4, 1626.9, 1607.9, 1594.8, 1560.7, 1363.7, 1276.8, 1271.6, 1267.0, 1223.9, 769.2 cm^{-1}; ^{1} HNMR (Me_2SO-d_6) δ 14.30 (br s, 1, H-4), 8.06 (s, 1, H-2'), 8.02 (d, 1, H-6'), 7.76 (m, 1, H-4'), 7.60 (t, 1, H-5'), 7.09 (br s, 1, H-3), 4.32 (q, 2, -OCH_2CH$_3$), 1.33 (t, 3, -OCH$_2$CH_3), also very weak multiplets at 4.62, 4.19, 1.22 for the unenolized tautomer. *Anal.* Calcd for $C_{12}H_{11}ClO_4$: C, 56.69; H, 4.33. Found: C, 56.56; H, 4.30.

Ethyl 4-(3-Nitrophenyl)-2,4-dioxobutyrate (84). Mp 73-74 °C; MS (FAB) *m/e* 266 (M + 1); IR (KBr) 3073.9, 2993.5, 1735.7, 1614.0, 1604.0, 1530.8, 1477.2, 1366.0, 1349.8, 1272.3, 1130.7, 1072.6, 1019.2, 781.5, 714.1, 673.4 cm^{-1}; ^{1} HNMR (Me_2SO-d_6) δ 8.71 (s, 1, H-2'), 8.51 (m, 1, H-6'), 8.51 (m, 1, H-4'), 7.87 (t, 1, H-5'), 7.18 (br s, 1, H-3), 4.35 (q, 2, $-OCH_2CH_3$), 1.33 (t, 3, $-OCH_2CH_3$), also very weak multiplets at 4.73, 4.25, 1.25 for the unenolized tautomer. *Anal.* Calcd for $C_{12}H_{11}NO_6$: C, 54.34; H, 4.15; N, 5.28. Found: C, 54.26; H, 4,16; N, 5.14.

Ethyl 4-(3-Methylphenyl)-2,4-dioxobutyrate (85). Mp 37-39 °C; MS (FAB) *m/e* 235 (M + 1); IR (KBr) 2987.5, 1976.2, 1729.1, 1627.3, 1597.9, 1591.2, 1579.2, 1518.2, 1511.5, 1470.9, 1444.2, 1364.8, 1270.7, 1257.7, 1175.5, 1115.6, 1108.2, 1085.5, 1029.0, 867.9, 770.2, 628.1 cm^{-1}; ^{1} HNMR (Me_2SO-d_6) δ 7.82 (br s, 1, H-2'), 7.80 (d, 1, H-6'), 7.45 (m, 1, H-5'), 7.45 (m, 1, H-4'), 4.40 (br s, 2, H-3'), 4.27 (q, 2, $-OCH_2CH_3$), 2.19 (s, 3, CH_3-3p), 1.29 (t, 3, $-OCH_2CH_3$), also very weak multiplet at 6.90 for the unenolized tautomer. *Anal.* Calcd for $C_{13}H_{14}O_4$: C, 66.67; H, 5.98. Found: C, 66.70; H, 6.04.

Ethyl 4-(3-Pyridyl)-2,4-dioxobutyrate (86) was prepared by adaptation of the general procedure from 3-acetylpyridine. Pure 73, mp 64-65 °C, gave the following characterization data. MS (FAB) *m/e* 221 (M + 1); IR (KBr) 3095 (w), 2975 (w), 2875 (w), 1732.6, 1630.1, 1605.9, 1590.5, 1422.3, 1317.4, 1295.9, 1260.7, 1125.9, 1027.0, 1016.1, 776.5, 696.7 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 9.22 (d, 1, H-2'), 8.84 (m, 1, H-4'), 8.43 (m, 1, H-6'), 7.62 (m, 1, H-5'), 7.16 (s, 1, H-3), 4.32 (q, 2, $-OCH_2CH_3$), 1.34 (t, 3 $-OCH_2CH_3$), very weak multiplets at 9.17, 8.71, 8.33, 4.67, 4.25, 2.14, 1.3 for the unenolized tautomer. Yield 35%. *Anal.* Calcd for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.43; N, 6.33. Found: C, 59.74: H, 5.09; N, 6.28.

Synthesis of Ethyl 3-Methyl-4-phenyl-2,4-dioxobutyrate 88.

Sodium methoxide (3.81 g, 70.6 mmol) was dissolved with stirring in 60 mL absolute EtOH. A solution of propiophenone (9 g, 67.06 mmol) in 30 mL EtOH was added dropwise over 1 h. The reaction mixture was stirred 1 h before a solution of ethyl oxalate (11.8 g, 80.8 mmol) in 20 mL EtOH was added dropwise over 20 min. The reaction mixture became cloudy and developed a bright yellow color during the addition. After 2 h of stirring at room temperature, the solution was evaporated to a yellow gum. The gum was treated with ice and water then acidified with conc. HCl. The reaction mixture was extracted with two portions of ether (300 mL, 100 mL). Extract and washings were pooled, washed with H_2O containing 2 mL

saturated $NaHCO_3$ solution, and then with saturated NaCl solution. The extract was dried, filtered and evaporated. The crude product was purified by flash chromatography using approximately 1200 g of silica gel. The column was developed with 20:1 hexane-ethyl acetate (HE) and the product was eluted with 9:1 HE. A remaining trace of an impurity was removed by rechromatographing the product (300 g silica). Yield, 2.1 g; MS (FAB) *m/e* 235 (M + H); IR (KBr) 1751, 1731, 1673, 1450, 1291, 1269, 1248, 1208, 1112, 1040, 708 cm^{-1}; ^1H NMR ($CDCl_3$) 1.29 (t, 3H, $-CH_2CH_3$), 1.47 (d, 3H, $-CHCH_3$), 4.27 (q, 2H, $-CH_2CH_3$), 5.05 (q, 1H, $-CHCH_3$), 7.51, 7.62, 7.99 (3 m, 5H, phenyl). *Anal.* Calcd for $C_{13}H_{14}O_4 \cdot 0.1H_2O$: C, 66.15; H, 6.06. Found: C, 66,18; H, 5.94.

4-(4-Methoxyphenyl)-2,4-dioxobutyric Acid (89). A solution of ethyl 4-(4-methoxy-phenyl)-2,4-dioxobutyrate (78) (2.00 g, 8.00 mmol) in EtOH (50 mL) containing KOH (2.0 g, 36 mmol) was kept at 20-25 °C for 3 days. The yellow solid that gradually formed was collected, washed with EtOH, and suction dried on the funnel. The solid was stirred with H_2O (25 mL) to give a partial solution. The mixture was kept in an ice-H_2O bath while it was stirred and carefully treated with 1 *N* HCl to lower the pH to 1. The precipitate that formed was collected, washed with H_2O, and dried *in vacuo* to give 89, mp 108 °C dec, in 85% yield (1.55 g). *Anal.* Calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.50. Found: C, 59.25; H, 4.58. Spectral data: Mass, *m/z* 222, M^+; ^1H NMR δ 3.88 (s, OCH_3), 7.00 and 8.07 (two d, C_6H_4).

4-(4-Nitrophenyl)-2,4-dioxobutyric Acid (90). A stirred suspension of 74 (2.00 g, 7.55 mmol) in 6 *N* HCl (100 mL) was kept at 80 °C for 16 h. The mixture was allowed to cool to room temperature, and stirring was continued two days longer before the insoluble solid present was collected, washed with H_2O, and dried *in vacuo*. This material proved to be pure 90, yield 64%; mp 167-173 °C dec, in 64% yield (1.15 g). *Anal.* Calcd for $C_{10}H_7NO_6$: C, 50.63; H, 2.95; N, 5.91. Found: C, 50.62, H, 3.06; N, 5.94. Spectral data (mass, ^1H NMR, IR) support the assigned structure.

General Procedure for the Preparation of the Phenyl-substituted 4-Phenyl-2,4-dioxobutyric Acids 91-95.[42-44]

A solution of the appropriate ethyl ester (3.0 g) in EtOH (50 ml) containing KOH (3.0 g) was kept at 20-25 °C for 3 days. The solid that gradually formed was collected, washed with fresh EtOH, and suction dried on the funnel. The solid was then stirred in H_2O (25 ml) to give a mixture which was carefully treated with 0.63 *N* HCl until the pH was lowered to 1. The resulting lighter-colored precipitate was collected,

washed with H_2O, and dried *in vacuo*. (When required, the compounds were further purified by readdition to H_2O, reacidifying with 0.63 *N* HCl to pH 1, and drying *in vacuo*.)

4-(3-Trifluoromethylphenyl)-2,4-dioxobutyric Acid (91). Yield, 86%; mp 131-132 °C; MS (FAB) *m/e* 261 (M + 1); *Anal.* Calcd for $C_{11}H_7O_4F_3$: C, 50.78; H, 2.71. Found: C, 50.72; H, 2.49.

4-(3-Fluoromethylphenyl)-2,4-dioxobutyric Acid (92). Yield, 83 %; mp 129-132 °C; MS (FAB) *m/e* 211 (M + 1); *Anal.* Calcd for $C_{10}H_7O_4F\ H_2O$: C, 52.63; H, 3.95. Found: C, 52.52; H, 3.85.

4-(3-Methoxyphenyl)-2,4-dioxobutyric Acid (93). Yield, 87%; mp 139-142 °C; MS (FAB) *m/e* 223 (M + 1); *Anal.* Calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.50. Found: C, 59.12; H, 4.41.

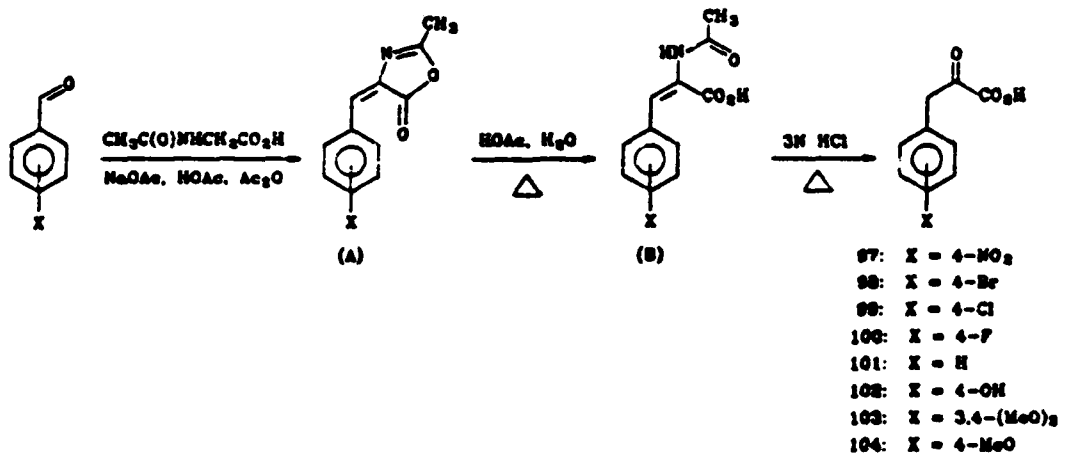
4-(3-Methylphenyl)-2,4-dioxobutyric Acid (94). Yield, 90%; mp 122-125 °C; MS (FAB) *m/e* 207 (M + 1); *Anal.* Calcd for $C_{11}H_{10}O_4\ H_2O$: C, 63.52; H, 4.91. Found: C, 63.41; H, 4.96.

4-(3-Chlorophenyl)-2,4-dioxobutyric Acid (95). Yield, 88%; mp 145-148 °C; MS (FAB) *m/e* 227 (M + 1); *Anal.* Calcd for $C_{10}H_9O_4Cl{\cdot}0.3H_2O$: C, 51.76; H, 3.30. Found: C, 51.64; H, 3.26.

Potassium 4-(2,4-Difluorophenyl)-2,4-dioxobutanoate (96). Ethyl 4-(2,4-difluorophenyl)-2,4-dioxobutanote (75) (2.0 g) was added to a solution of KOH (2.0 g) in EtOH (50 mL). The solution was stirred at 20-25 °C, and, after 3 days, a white precipitate had formed. The salt was collected, washed with EtOH, and dried *in vacuo* to give 96. Yield, 95%; mp 215 °C dec. *Anal.* Calcd for $C_{10}H_5F_2KO_4$: C, 55.17; H, 4.98. Found: C, 54.97; H, 4.83. Spectral data: MS (FAB) *m/e* 266 (M-H); ^{1}H NMR (Me_2SO-d_6) δ 7.79 (q, 1, H-2'), 7.29 (m, 1, H-3'), 7.15 (m, 1, H-5'), 5.60 (s, 2, H-3), also very weak multiplets at 8.07, 7.60, 4.12, 2.70, 2.40 for the unenolized tautomer.

B. DERIVATIVES OF 3-PHENYL-2-OXOPROPIONIC ACID.

As a second class of carbonyl-containing compound capable of cyanide detoxification, we chose to prepare the series of substituted phenylpyruvates shown below. The synthesis of these substances was based upon literature methods, beginning with a substituted benzaldehyde as shown in the following equations. Condensing the benzaldehyde with *N*-acetylglycine gave oxazolinone (A) which was then treated with acid to cleave the ring, yielding the desired pyruvic acid derivative. Table 9 summarizes the data obtained for these compounds.



General Synthesis of Substituted Phenyl Pyruvates (3-Phenyl-2-oxopropionates).

A solution of *N*-acetylglycine (7.0 g, 60 mmol) in 20 mL acetic acid and 21 mL acetic anhydride containing sodium acetate (14.4 g, 176 mmol) and 64 mmol of a substituted benzaldehyde was stirred at 100 °C for 2 hrs. After the solution was cooled to 10 °C, 100 mL H_2O was added with vigorous stirring. The resulting precipitate (A) was collected by filtration.

A solution of A in 150 mL HOAc was heated to 100 °C. Five mL H_2O was added and the solution stirred at 100 °C for 15 min. Upon allowing the solution to cool slowly to room temperature, a precipitate formed (B). In cases where no precipitate formed, the solution was then stripped to dryness to obtain B. The suspension of B in 150 mL 3 *N* HCl was then stirred at reflux for 7 hrs. After the mixture was cooled to 0 °C, the product C was collected by filtration and washed with cold H_2O and dried under vacuum.

3-(4-Nitrophenyl)pyruvic acid 97 (exists prima ily in enolized form).

Mp 182-184 °C; MS (neg. fab) *m/e* 208 (M - 1); IR (KBr) 3475.7, 3473.2, 3075.0, 1975.0, 1765.0, 1681.4, 1591.7, 1512.5, 1446.6, 1324.6, 1316.4, 1244.4, 1205.1, 875.36, 862.92 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 13.60 (br s, 1H, H^+) 10.26 (br s, 1H, H^+), 8.19 (n, 2H, H-3'), 7.98 (m, 2H, H-2'), 6.54 (s, 1H, H-3). There was also a small signal (1/14 the intensity of the peak at 6.54) at 4.38 for the unenolized tautomer. *Anal.* Calcd for $C_9H_7NO_5$: C, 51.67; H, 3.35; N, 6.70. Found: C, 51.84; H, 3.32; N, 6.55.

3-(4-Bromophenyl)pyruvic acid 98 (exists primarily in enolized form).

Mp 177-185 °C; MS (neg FAB) *m/e* 242 (M - 1); IR (KBr) 3467.8, 3465.8, 1905.9, 1685.4, 1649.5,

1444.0, 1219.7, 1200.0, 1074.9 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 13.26 (br s, 1H, H^+), 9.48 (br s, 1H, H^+), 7.71 (m, 2H, H-3'), 7.53 (m, 2H, H-2'), 6.37 (s, 1H, H-3). There was a small signal (1/14 the intensity of the peak at 6.37) at 4.15 for the unenolized tautomer. *Anal.* Calcd for $C_9H_7BeO_3$: C, 44.44; H, 2.88. Found C, 44.49; H, 2.87.

TABLE 9. 3-PHENYL-2-OXOPROPIONATES.

Structure No.	Yield, %	Mp, °C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd Found %C	%H	%N
97	89	182-184	$C_9H_7NO_5$ (209.157)	51.67	3.35	6.70
98	82	177-185	$C_3H_7BrO_3$ (243.06)	4.44 44.49	2.88 2.87	
99	94	183-187	$C_9H_7ClO_3$ (198.61)	54.41 54.08	3.53 3.43	
100	66	151-156	$C_9H_7FO_3$ (182.15)	59.34 59.46	3.85 3.88	
181	60	141-145	$C_9H_8O_3$ (164.16)	65.85 66.02	4.88 5.07	
102	Purchased from Aldrich	204-205	$C_9H_8O_4$ (180.16)	60.00 60.00	4.44 4.45	
103	66	175-182	$C_{11}H_{12}O_5$ (224.21)	58.93 58.91	5.36 5.42	
104	81	180-185	$C_{10}H_{10}O_4$ (194.19)	61.85 61.90	5.19 5.27	

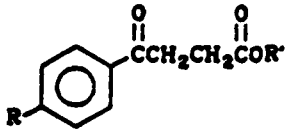
3-(4-Chlorophenyl)pyruvic acid 99 (exists primarily in enolized form).

Mp 183-187 °C; MS (neg FAB) *m/e* 197 (M - 1); IR (KBr) 3465.9, 1911.3, 1679.8, 1664.2, 1436.1, 1409.5, 1225.2, 1201.5, 1088.7, 867.55, 821.10 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 13.31 (br s , 1H, H^+), 9.47 (br s, 1H, H^+), 7.78 (m, 2H, H-3'), 7.40 (m, 2H, H-2'), 6.39 (s, 1H, H-3). There was a small signal (1/14 the intensity of the peak at 6.39) at 4.18 for the unenolized tautomer. *Anal.* Calcd for $C_9H_7ClO_3$: C, 54.41; H, 3.53. Found: C, 54.08; H, 3.43.

C. DERIVATIVES OF 4-PHENYL-4-OXOBUTYRIC ACID.

Another selected class of carbonyl-containing compound capable of cyanide detoxification, were the

phenylbutyrates shown below (105-107). The synthesis of the two esters was based upon literature methods,[32] by treating either benzaldehyde or 3-bromobenzaldehyde with an α,β-unsaturated carbonyl derivative in the presence of sodium cyanide, as shown below. Carboxylic acid 107 was a commercial sample (Aldrich Chemical Co., Milwaukee, WI). Table 10 summarizes the data obtained for these compounds.



	R	R'
105:	H	C_2H_5
106:	Br	C_2H_5
107:	H	H

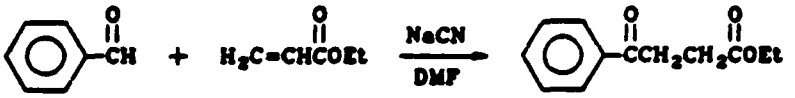
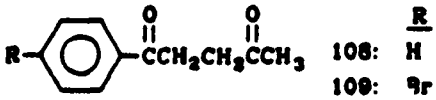


TABLE 10. 4-PHENYL-4-OXOBUTYRATES

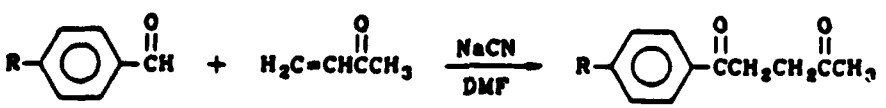
Structure No.	Yield, %	Mp, °C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd / Found %C	Elemental Analyses Calcd / Found %H
105	13	Oil	$C_{12}H_{14}O_3$ (206.23)	69.90 / 70.07	6.80 / 6.74
106	46	54-57	$C_{12}H_{13}O_3Br$ (285.12)	50.51 / 50.59	4.56 / 4.65
107	Purchased (Aldrich)	117-119	$C_{10}H_{10}O_3 \cdot 0.1H_2O$ (180.0)	66.73 / 66.40	5.72 / 5.52

D. MISCELLANEOUS CARBONYL DERIVATIVES.

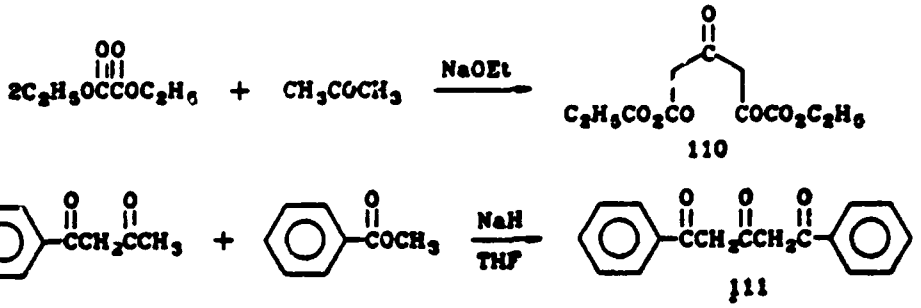
Four additional carbonyl- or polycarbonyl-containing compounds of varying structural types were prepared and submitted during this report period. Compounds 108 and 109 were prepared in a similar fashion to 105 and 106, employing methyl vinyl ketone in the condensation in place of ethyl acrylate, as shown in the following equation.[32]



	R
108:	H
109:	Br



The triketones 110 and 111 were also submitted; these derivatives were prepared through the base-catalyzed condensations of methyl ketone precursors as depicted below.[33,34]



General Procedure for Synthesis of 4-Phenyl-4-oxobutyrate Esters.

A solution of the appropriately substituted benzaldehyde (0.05 mol) in anhydrous DMF (50 mL) was added dropwise to a stirred mixture of sodium cyanide (0.025 mol) in DMF (50 mL) at 35 °C under nitrogen. After 5 min, a solution of ethyl acrylate (0.0375 mol) in DMF (50 mL) was added over a 20 min period, with the temperature maintained at 35 °C. Stirring was continued for 3 hr. The solution was then treated with two volumes of H_2O. After repeated extractions with $CHCl_3$, the pooled extracts were washed with 3 *N* HCl, saturated $NaHCO_3$ solution, and finally with H_2O. After removal of the solvent the residue was purified by column chromatography.

Table 11 summarizes the physical properties of these four miscellaneous carbonyl compounds.

TABLE 11. MISCELLANEOUS POLYCARBONYL DERIVATIVES

Structure No.	Yield, %	Mp, °C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd Found	
				%C	%H
108	68	Oil	$C_{11}H_{12}O_2$ (176.21)	75.00 74.67	6.82 7.09
109	49	78-81	$C_{11}H_{11}O_2Br$ (255.10)	51.76 51.72	4.31 4.28
110	52	98-100	$C_{11}H_{14}O_7$ (258.22)	51.16 51.13	5.46 5.49
111	72	105-108	$C_{17}H_{14}O_3$ (266.30)	76.68 76.42	5.30 5.17

Ethyl 4-phenyl-4-oxobutyrate (105). MS (FAB) *m/e* 207 (M + 1); IR (KBr) 3063.5, 2984.8, 2250.1, 1734.4, 1688.5, 1449.1, 1375.4, 1364.4, 1349.2, 1263.7, 1244.7, 1218.7, 1179.4, 1166.8, 749.71, 691.43 cm^{-1}. *Anal.* Calcd for $C_{12}H_{14}O_3$: C, 69.90; H, 6.80. Found: C, 70.07; H, 6.74.

Ethyl 4-(4-bromophenyl)-4-oxobutyrate (106). MS (FAB) *m/e* 285 (M + 1); mp 54-57 °C; IR (KBr) 985.5, 2979.1, 1729.4, 1670.8, 1583.4, 1423.0, 1400.3, 1320.6, 1305.6, 1185.8, 1176.6, 1069.1, 989.33, 788.72 cm^{-1}. *Anal.* Calcd for $C_{12}H_{13}O_3Br$: C, 50.51; H, 4.56. Found: C, 50.69; H, 4.65.

General Procedure for Synthesis of 1-Phenyl-1,4-pentanediones.

A solution of the appropriate substituted benzaldehyde (0.1 mol) in anhydrous DMF (50 mL) was added dropwise to a stirred mixture of sodium cyanide (0.01 mol) in DMF (50 mL) at 35 °C under nitrogen. After stirring 5 min, a solution of freshly distilled methyl vinyl ketone (0.048 mol) in DMF (50 mL) was added over a 20 min period, with the temperature maintained at 35 °C. Stirring was continued for 1 h. The reaction mixture was then treated with two volumes of H_2O. After repeated extractions with $CHCl_3$, the combined extracts were wasned with 3 *N* HCl, saturated $NaHCO_3$ solution, and finally with H_2O. After removal of the solvent, the residue was vacuum distilled and further purified by column chromatography.

1-Phenyl-1,4-pentanedione (108). MS (FAB) *m/e* 177 (M + 1); IR (KBr) 1710.0, 1686.0, 1596.6, 1448.9, 1398.9, 1359.9, 1242.7, 1212.5, 1163.1, 1001.8, 746.13, 691.15, 349.11 cm^{-1}; *Anal.* Calcd for $C_{11}H_{12}O_2$: C, 75.00; H, 6.82. Found: C, 74.67; H, 7.09.

1-(4-Bromophenyl)-1,4-pentanedione (109). MS (FAB) *m/e* 255 (M + 1); mp 78-81 °C; IR (KBr) 1707.6, 1677.4, 1585.6, 1567.3, 1408.3, 140.01, 1389.8, 1352.8, 1315.8, 1209.9, 1070.0, 992.41, 847.90, 826.99 cm^{-1}; *Anal.* Calcd for $C_{11}H_{11}O_2Br$: C, 51.76; H, 4.31. Found: C, 51.72; H, 4.28.

Procedure for the Preparation of Diethyl-2,4,6-trioxoheptanedioate (110).

Freshly cut Na (4.6 g, 0.2 mol) was added to absolute ethanol (100 mL) under nitrogen. The mixture was stirred until the Na had completely dissolved. Approximately one-half of the sodium ethoxide solution was poured into a screw-top Erlenmeyer and kept at 60 °C, 5.8 g (0.1 mol) of acetone mixed with 15 g (0.103 mol) diethyl oxalate was added in one portion to the stirred sodium ethoxide solution at room temperature, resulting in a thick yellow slurry. The heated sodium ethoxide solution was then poured into the slurry, together with 16 g (0.11 mol) diethyl oxalate, the two streams being allowed to mix as they flowed into the

flask. The reaction was allowed to stir at room temperature for 45 min. The flask was then equipped with a distillation condenser and heated in an oil bath until approximately 25 mL EtOH had distilled. The flask was then allowed to cool to room temperature. The slurry was poured into a large beaker over 80 g cracked ice, then acidified with 30 mL concentrated HCl. The mixture was stirred until the ice had melted and the resulting yellow precipitate was collected by filtration washed several times with H_2O, and dried *in vacuo*.

Diethyl-2,4,6-trioxoheptanedioate (110). Yield, 52%; MS (FAB) *m/e* 259 (M + 1); IR (KBr) 3106.4, 2982.9, 1732.9, 1644.2, 1634.5, 1406.1, 1388.2, 1370.9, 1337.6, 1277.2, 1266.2, 1136.6, 1122.1, 1116.1, 1109.3, 1030.8, 878.22, 869.34, 820.30, 783.36, 716.09, 613.54 cm^{-1}; *Anal.* calcd. for: $C_{11}H_{14}O_7$. C, 51.16; H, 5.47. Found: C, 51.13; H, 5.49.

1,5-Diphenyl-1,3,5-pentanetrione (111).

A well stirred suspension of NaH (4.8 g, 0.2 mol; 60% suspension in mineral oil, 8 g) in 100 mL dry THF under argon was heated at gentle reflux and treated with a solution of benzoylacetone (6.5 g, 0.04 mol) and methylbenzoate (8.2 g, 0.06 mol) in 100 mL THF over 1 1/2 h. After a further 1 h reflux, the reaction was checked by TLC. Benzoylacetone remained so 1 mL additional methylbenzoate was added, followed by 2 h reflux. The reaction mixture was cooled and stored at room temperature overnight, then concentrated to a small volume at reduced pressure and taken up in ~200 mL ether. The ether solution was treated with ~200 mL H_2O (initially dropwise-vigorous). The organic layer was separated, washed with 100 mL H_2O, then 100 mL 1% NaOH, and pooled the aqueous extracts back washed with 150 mL ether. The aqueous phase was chilled in ice bath, ice added to the solution, which has then acidified with concentrated HCl (30 mL). The product, which crystallized, was collected; yield 8.7 g (82%). One recrystallization from hot EtOH yielded 6.8 g (72%). Mp 105-108 °C shining yellow platelets. MS (FAB) *m/e* 267 $(M + H)^+$; 147 $(M - OCOCH_2)$; IR (KBr) 1603, 1595, 1567, 1538, 1493, 1450, 1378, 1280, 1163, 1157, 895, 775, 690, 685 cm^{-1}; ^1H NMR ($CDCl_3$) (mixture of ketone, enol isomers) δ 14.75 (s, 1-2, enol-OH), 7.4-7.9 (2m, 10, aromatic H), 6.31 (s, 1, C(OH)=*CH*C(O)), 6.02 (s, 2, enol; CH), 4.11 (s, 2, CH_2). *Anal.* Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.42; H, 5.17.

V. METAL COMPLEXES

We also embarked on a synthetic program to explore the utility of metal complexes, including

porphyrins, phthalocyanines, and inorganic cobalt species, for cyanide antagonism. Our premise for this approach was that we could select metal ions with high affinities for cyanide and attempt to reduce the toxicity of these metals by sequestering them in suitable water-soluble complexes. Thus, simple EDTA complexes of cobalt are already employed as cyanide antidotes in several countries, and therefore, we felt that these EDTA complexes supported further investigation of this concept. After consultation with the Contract Officer, we submitted four cobalt salts (112-115) based upon our belief that the combination of cobalt with counterions that might also detoxify cyanide, such as nitrite or thiosulfate, might be doubly expedient. One of the submitted compounds, SRI 8622, was a commercial product purchased from Aldrich Chemical Co., Milwaukee, WI. We also prepared the five additional systems depicted below (116-120); unfortunately, no biological data has been received for any of our metal complexes, so further synthetic activity in this area was suspended. The physical properties and structures of some of these compounds are also presented in Table 12 and the following page.

EXPERIMENTAL SECTION FOR PART V.

Hydroxycobaltoushydroxycobaltinitratenitrite (112).[36]

$$HNO_3 + As_2O_3 \longrightarrow N_2O_3 \xrightarrow[H_2O]{CoCO_3} Co^{+2}_4Co^{+3}_2(NO_2)_8(NO_3)_2(OH)_4 \cdot XH_2O$$

SoRI 8620.

The procedure of Suzuki was repeated. Arsenic(III) oxide (30 g) was treated dropwise with conc HNO_3. As enough liquid became available the mixture was stirred and warmed to 50-55 °C and a slow stream of argon was used to facilitate the generation and transfer of dinitrogen trioxide; this gas in turn was bubbled into a stirred aqueous suspension of $CoCO_3$ until it almost completely dissolved. The insoluble $CoCO_3$ was removed by filtration and the filtrate was evaporated *in vacuo* below 30 °C. Yield, 4.0 g; IR (KBr) 1389, 1356 cm^{-1}.

Potassium Cobaltous Tetranitrite (113).[36]

$$CoCl_2 + KNO_2 \longrightarrow Co(NO_2)_2 \cdot 2KNO_2 \cdot H_2O$$

SoRI 8621.

The reaction described by Remy was repeated as follows:

Cobaltous(II) chloride (5 g, 38.5 mmol) was dissolved in 75 mL H_2O. The KNO_2 (13.1 g, 0.15 mol) dissolved in 25 mL H_2O was added to the reaction solution with stirring. The mixture became turbid, and after standing at room temperature 20 min was filtered to provide a clear solution. Addition of some ethanol facilitated the formation of a yellow precipitate, which was collected, washed with additional ethanol, and dried *in vacuo* over phosphorus pentoxide. Yield, 7.9 g; IR (KBr) 1395, 1334, 829 cm^{-1}.

TABLE 12. METAL COMPLEXES

Structure No.	Yield, %	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd Found %C	%H	%N
112	--	Remarks: This compound has not been characterized. The literature procedure was followed and we assume the product to be as described.			
113	--	Remarks: This compound has not been characterized. The literature procedure was followed and we assume the product to be as described.			
114 (Commercial Sample)	--	Remarks: This compound has not been characterized. The literature procedure was followed and we assume the product to be as described.			
115	87	Remarks: This compound has not been characterized. The literature procedure was followed and we assume the product to be as described.			
116	--	$C_{32}H_{12}N_8O_{12}S_4Na_4Ni{\cdot}4H_2O$ (1,051.45)	36.55 36.17	1.91 1.99	10.65 11.63
117	--	$C_{32}H_{12}N_8O_{12}S_4Na_4Mn{\cdot}6H_2O$ (1,083.74)	36.20 36.00	2.37 2.00	10.45 10.45
118	--	$C_{44}H_{28}N_8O_{12}Mn{\cdot}4.5H_2O$ (996.73)	49.43 49.63	3.48 3.20	5.23 4.87

Cobalt(II) Thiosulfate (115).[37]

$$CoSO_4 + BaS_2O_3 \xrightarrow[H_2O]{} CoS_2O_3 + BaSO_4\downarrow$$

SoRI 8623.

A filtered solution of cobalt sulfate (3.2 g, 18.7 mmol) in 50 mL of hot water was added to a filtered

solution of barium thiosulfate (5 g, 18.7 mmol) in ~800 mL of warm water. The mixture was stirred well and stored at 5 °C overnight. The white precipitate, which had formed immediately, was removed by filtration through a celite pad. The filtrate was evaporated to dryness *in vacuo* below 30 °C. The product was dried *in vacuo* at room temperature over phosphorus pentoxide. Yield, 2.8 g (black to dark blue powder); IR (KBr) rounded peaks 3425, 1625, 1140, 1110, 650 cm^{-1}.

Synthesis of Tetraammoniumtetra(*p*-sulfophenyl)porphine. Tetraphenylporphine (2.0 g) was suspended in concentrated H_2SO_4 (50 mL), heated on a steam bath for 6 h, then allowed to stand at room temperature overnight. The mixture was diluted with two volumes of water. The resulting bright green precipitate was filtered and washed with acetone. The residue was transferred to a beaker and dissolved in 150 mL of methanolic ammonia; impurities were filtered out. The sulfonated porphyrin was precipitated from the filtrate with three volumes of acetone, then reprecipitated six times from methanol and acetone. The product was finally dried under reduced pressure over P_2O_5. Anal. Calcd for $C_{44}H_{38}N_8O_{12}S_4 \cdot 9H_2O$: C, 44.23; H, 4.17; N, 9.66. Found: C, 44.26; H, 4.18, N, 9.46.

Synthesis of tetraphenylporphyrin tetrasulfonates, tetrasodium Salts. Tetraphenylporphine (2.0 g) was suspended in concentrated H_2SO_4 in a 250 mL RB flask, equipped with a condenser and drying tube. The mixture was heated on a steam bath for 6 h and then left overnight. The viscous green mixture was diluted carefully with water (150 mL) and was allowed to cool to room temperature. The green precipitate was collected by filtration and washed with acetone. The residue was suspended in 150 mL of water with celite, and slowly neuterlized with a saturated solution of sodium carbonate until the green precipitate turned purple. The mixture was then filtered to remove celite and unreacted tetraphenylporphine. The water was removed under reduced pressure. The residue was dissolved in methanol, filtered, and the residue washed with methanol, to remove the impurities. The methanol was removed and the residue again dissolved in methanol and filtered. This procedure was repeated 4 times to generate the pure product. Anal. Calcd for $C_{44}H_{26}N_4O_{12}S_4Na_4 \cdot 12H_2O$: C, 42.68; H, 4.06; N, 4.52. Found: 42.65; H, 4.17; N, 4.33.

Preparation of Tetrasodium Salt of Manganese (II) and Nickel(II) tetrasulfophthalocyanine (117 and 116). This procedure is adapted from the method of Weber and Busch.[40]

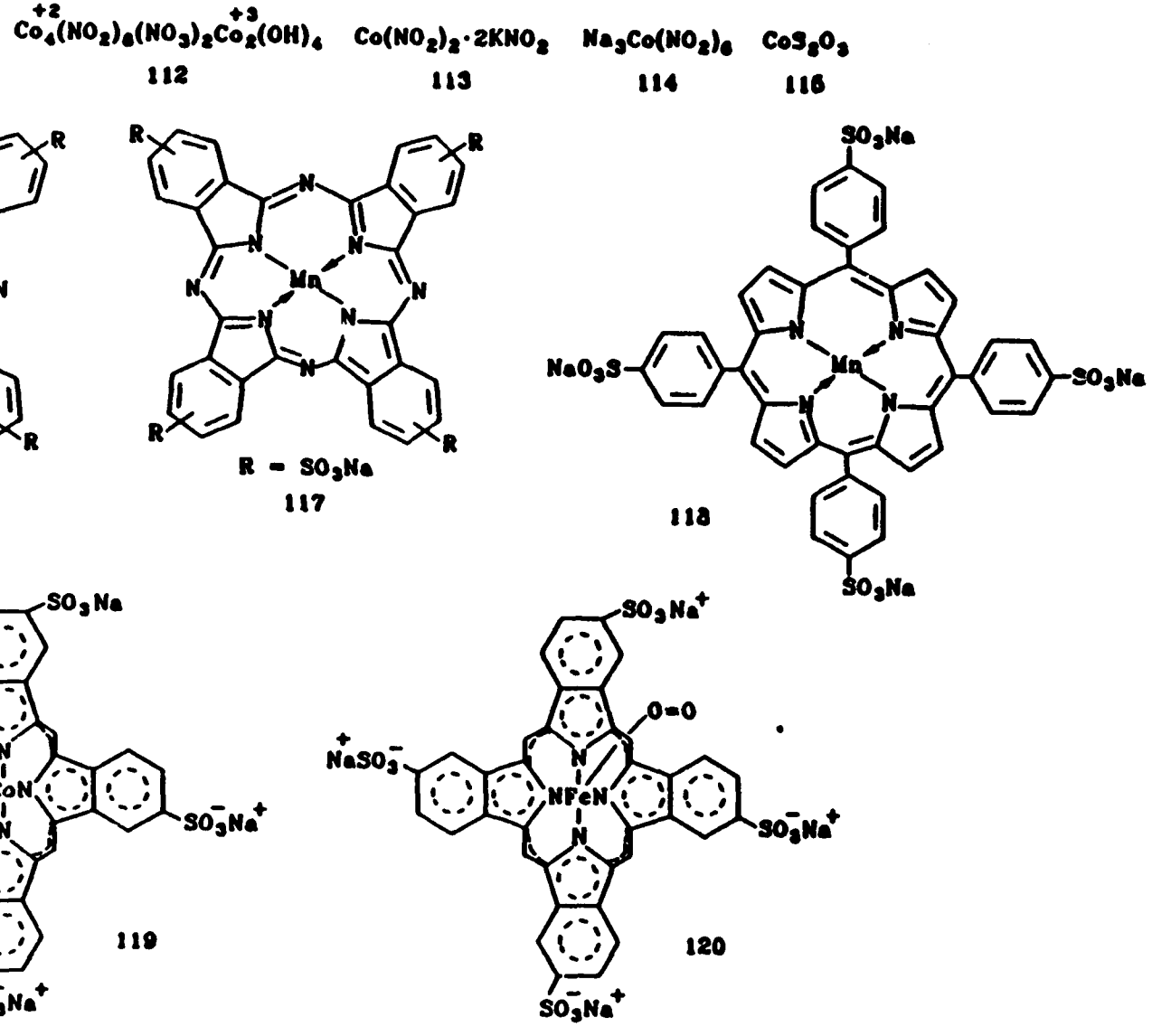
The monosodium salt of 4-sulfophthalic acid (0.04 mol), ammonium chloride (0.02 mol), urea (0.24

mol), ammonium molybdate (0.00015 mol), and metal acetate (0.012 mol) were ground together until homogeneous. The solid mixture was heated slowly to 180 °C. The heating was continued for 6 h, maintaining a temperature between 180-190 °C The crude solid product was ground and added to 300 mL of 1 *N* HCl, saturated with sodium chloride. This step is crucial for the removal of excess manganese salt from the product. The solution and accompanying undissolved material were briefly heated to boiling, cooled to room temperature, and filtered. The resulting solid was dissolved in 200 mL of 0.1 *N* NaOH. The solution was then heated to 80 °C and insoluble impurities were immediately separated. Sodium chloride (68.0 g) was added to the solution and heated to 80 °C until ammonia evolution was complete. Product 117 was obtained by filtration, and washed with 80% ethanol until the filtrate was chloride free. This product was refluxed in 100 mL of absolute alcohol, and the product filtered and dried over P_2O_5. Anal. Calcd for $C_{32}H_{12}N_8O_{12}S_4Na_4Mn{\cdot}6H_2O$: C, 36.20; H, 2.37; N, 10.45. Found: C, 36.00; H, 2.00; N, 10.45.

Nickel sulfophthalocyanine (116) was prepared by essentially the same proceudre. Anal. Calcd for $C_{32}H_{12}N_8O_{12}S_4Na_4Ni{\cdot}4H_2O$: C, 36.55; H, 1.91; N, 10.65. Found: C, 36.17; H, 1.99; N, 10.63.

Preparation of Manganese(III) (4-Sulfophenyl)porphine (118). Manganese acetate (2.5 g) and tetra(ammonium sulfophenyl)porphine (1.0 g) were dissolved in 80 mL of water and heated at 80 °C for 24 h. After cooling, the solution was evaporated to ~20 mL and passed through a Dowex 50-WX8 cation exchange column. The eluate was evaporated to dryness, dissolved in ethanol, and re-evaporated under reduced pressure. The product was redissolved in water, and passed through G-10 sephadex to remove inorganic impurities. The material was then dried under reduced pressure over P_2O_5. UV in water, λ_{max} 466, ϵ 92.9 x 10^{-3} mol^{-1} cm^{-1}. Anal. Calcd for $C_{44}H_{28}N_8O_{12}Mn{\cdot}4.5H_2O$: C, 49.43; H, 3.48; N, 5.23. Found: C, 49.63; H, 3.20; N, 4.87.

Synthesis of Cobalt Sulfophthalocyanine (119).[41] The monosodium salt of 4-sulfophthalic acid (0.04 mol), ammonium chloride (0.23 mol), urea (0.25 mol), ammonium molybdate (0.0002 mol), and cobalt sulfate (0.12 mol) were ground together and heated to 120-140 °C for 30 min; subsequently, the temperature was raised to 180-200 °C for 4 h. The resulting residue was powdered and then added to a saturated solution of NaCl in 1 *N* HCl (300 mL). This solution was heated to 70 °C, cooled to room temperature, and filtered. The residue was dissolved in 0.1 *N* NaOH solution (250 mL), heated to 80 °C and filtered quickly. NaCl (125 g)


$Co_4^{+2}(NO_2)_8(NO_3)_2Co_2^{+3}(OH)_4$
112
$Co(NO_2)_2 \cdot 2KNO_2$
113
$Na_3Co(NO_2)_6$
114
CoS_2O_3
115
R = SO_3Na
116
R = SO_3Na
117
SO_3Na
NaO_3S
SO_3Na
SO_3Na
118
SO_3Na
$NaSO_3^-$
NCoN
$SO_3^-Na^+$
$SO_3^-Na^+$
119
SO_3Na^+
$NaSO_3^-$
O=O
NFeN
$SO_3^-Na^+$
$SO_3^-Na^+$
120

was added to the filtrate, which was reheated to 80 °C for 2 h. The product precipitated after cooling, and was filtered, washed with 80% ethanol until chloride free, then refluxed for 4 h in absolute alcohol (50 mL). After another filtration the product was dried under reduced pressure over P_2O_5. Yield 72%. Anal. Calcd for $C_{32}H_{12}N_8O_{12}S_4Na_4Co{\cdot}2H_2O$: C, 37.82; H, 1.59; N, 11.03. Found: C, 37.14; H, 1.69; N, 11.43.

Synthesis of Fe(II) Sulfothalocyanine (120).[41]

The monosodium salt of 4-sulfophthalic acid (0.04 mol), ammonium chloride (0.023 mol), urea (0.25 mol), ammonium molybdate (0.0002 mol), and iron sulfate (0.012 mol) were ground together. Nitrobenzene (10 mL) was heated to 180 °C in a three neck flask fitted with condenser and thermometer. The solid mixture was added slowly with stirring while keeping the temperature between 160-190 °C. The heterogeneous mixture was heated 6 h at 180 °C. The crude product, a solid cake, was ground and washed with methanol until the nitrobenzene filtrate was no longer discolored. The remaining solid was added to 275 mL of 1 *N* HCl saturated with sodium chloride. The solution and accompanying undissolved material were briefly heated to boiling, cooled to room temperature, and filtered. The resulting solid was dissolved in 200 mL of 0.1 *N* NaOH. The solution was heated to 80 °C and insoluble impurities were immediately separated by filtration. Sodium chloride (135 g) was added to the solution. At this point some of the solid product precipitated. The slurry was again heated and stirred at 80 °C until ammonia evolution stopped. The product was obtained by filtration. The solid was washed with 80% aqueous alcohol until the filtrate was chloride free. The product was refluxed for 5 h in 100 mL of absolute alcohol. The pure product was obtained, filtered, and dried overnight *in vacuo* over P_2O_5. MS (neg. FAB) *m/e* (M^-), 977, (M - Na), 955; (M - 2Na), 933, (M - 3Na), 911, (M - 4Na), 888. *Anal.* Calcd for $C_{32}H_{16}N_8O_{16}S_4Na_4Fe{\cdot}3H_2O$: C, 37.20; H, 1.95; N, 10.85. Found: C, 36.3; H, 1.95; N, 11.00.

VI. SULFUR CONTAINING COMPOUNDS

A. TETRASULFIDES DERIVED FROM CARBOXYLIC ACIDS.

1. Derivatives of Thioglycolic and Thiolactic Acids.

2,2'-Tetrathiobisacetic acid (121) were prepared by treatment of the corresponding thio acid, thioglycolic acid or thiolactic acid, with sulfur monochloride (S_2Cl_2) in diethyl ether according to a reported procedure.[18] The dibenzyl ester 123 was prepared from 121 by direct esterification with benzyl alcohol

according to a reported procedure.[19]

121: R = H
122: R = CH_3

123

2. Tetrasulfide Derivatives of Cysteine

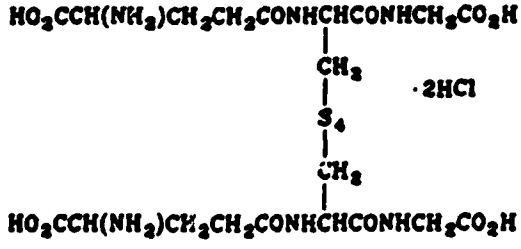
The tetrasulfide compounds corresponding to cysteine and also its diethyl ester and *N*-acetyl derivative were synthesized. Structures of these compounds (124-126) are shown below. In these preparations, we found S_2Cl_2 to be compatible with glacial AcOH, and this solvent was used to advantage since the starting thiols are insoluble in diethyl ether.

124: R = H
125: R = Et

126

3. Tetrasulfide Analogue of Glutathione.

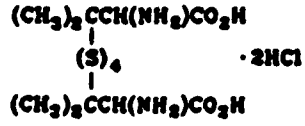
Reduced glutathione (Aldrich Chemical Co.) was treated with S_2Cl_2 in glacial AcOH in a successful preparation of the corresponding tetrasulfide 127 shown below.



127

4. 3,3'-Tetrathiobis-DL-valine.

Treatment of DL-penicillamine (Aldrich) with S_2Cl_2 in AcOH afforded the tetrathio derivative 128.

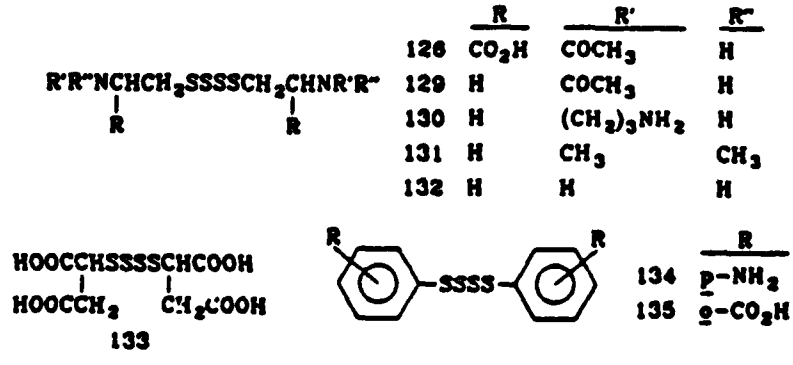


128

5. Other Tetrasulfide Compounds.

The favorable biological evaluation of 126 (SRI 7638; WR 268831) inspired an expanded effort directed toward the systematic exploration of the structure-activity profile of analogous tetrasulfide derivatives. A supplemental sample of the active agent was requested by and prepared for the CO for further evaluation and seven other novel examples were also prepared and submitted. In addition, the synthesis of numerous other compounds was begun, but not completed because these products could not be fully purified and characterized prior to the expiration of this project. The structures of these compounds are illustrated below. Physical data is for the seven new compounds reported in Table 13.

Compounds 129-132 share the *bis*-aminoethyl tetrasulfide motif of active cysteine derivative 126, the degree of substitution of the amino and methylene moieties being varied. Structures 133 and 135 were prepared to examine the requirement for the basic amino group, while 130, 131, 132, and 134 probed the necessity of the α-carboxylic acid. Finally, structures 134 and 135 examined the effect of replacement of the ethylene bridge with the planar, aromatic phenylene surrogate. Complete synthetic protocols for these compounds are in the experimental section.



EXPERIMENTAL SECTION FOR PART VI.A.

Tetrathiobisacetic Acid (121). A stirred solution of mercaptoacetic acid (1.56 g, 20 mmol) in $CHCl_3$ (50 mL) was treated with a 1 *M* solution of S_2Cl_2 in CH_2Cl_2 (10 mL, 10 mmol). The reaction mixture was stirred under N_2 for 30 min. The white solid that separated was collected, washed with $CHCl_3$ and dried *in vacuo*; yield 1.86 g (76%), mp 105-108 °C. MS (FAB) *m/e* 247 $(M + H)^+$; IR (KBr) 2800-3300 (broad), 1734, 1678, 1426, 1271, 1255, 1126, 1117 cm^{-1}; ^1H NMR (CD_3CN) δ 3.78 (s, 4, CH_2). *Anal.* Calcd for $C_4H_6O_4S_4$: C, 19.50; H, 2.46. Found: C, 19.58; H, 2.43.

TABLE 13. TETRASULFIDE COMPOUNDS

Structure No.	Yield, %	Mp, °C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd Found		
				%C	%H	%N
126*	18	134-137	$C_{10}H_{16}N_2O_6S_4$ (388.52)	30.91 30.99	4.15 3.92	7.21 7.02
129	71	90-92	$C_8H_{16}O_2S_4N_2$ (373.40)	25.73 25.74	4.85 4.94	7.50 7.41
130	95	218-220	$C_{10}H_{26}N_4S_4 \cdot 4HCl$ (330.37)	25.21 25.48	6.35 6.46	11.76 11.62
131	65	172-174	$C_8H_{20}N_2S_4 \cdot HCl \cdot 5H_2O$ (317.98)	30.21 30.47	6.97 7.08	8.88 8.57
132	58	155-157	$C_4H_{12}N_2S_4 \cdot 2HCl$ (289.33)	16.60 16.85	4.88 4.96	9.68 9.82
133	35	188-192	$C_8H_{10}O_8S_4$	26.51 26.84	2.78 2.55	- --
134	84	64-65 (dec.)	$C_{12}H_{12}N_2S_4 \cdot 2HCl \cdot H_2O$ (403.40)	35.73 35.68	4.00 3.96	6.94 6.60
135	86	--	$C_{14}H_{10}O_4S_4$	45.39 45.34	2.72 2.70	-- --

*Re-synthesis of an active, previously submitted sample.

Tetrathiobisacetic acid, dibenzyl ester (123). — A mixture of 77 (1.23 g, 5.0 mmol) and anhydrous benzyl alcohol (1.18 mL, 11.37 mmol) containing concentrated H_2SO_4 (0.07 mL was stirred at 20-25 °C for 7 days. This thick oil was placed on a silica gel column and eluted with chloroform. The fractions containing the product (UV detection) were combined and concentrated under reduced pressure to give an oil that was dried *in vacuo* for 1 h at 20-25 °C; yield 1.82 g (85%). MS (FAB) *m/e* 427 $(M + H)^+$; IR (film) 2800-3100 (broad), 1734, 1455, 1376, 1269, 1143, 1120, 994, 970, 745, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (m, 10, phenyl protons, 5.18 (s, 4, CH_2-O), 3.72 (s, 4, CH_2-S). *Anal.* Calcd for $C_{18}H_{18}O_4S_4$: C, 50.68; H, 4.25. C, 50.42; H, 4.33.

2,2-Tetrathiobispropanoic Acid (122). A solution of thiolactic acid (6.36 g, 60.0 mmole) in Et_2O (150 mL) was treated at 20-25 °C with a solution of S_2Cl_2 in CH_2Cl_2 (30 mL, 1 *M*). The reaction solution was

stirred at 20-25 °C for 1 h, and then the solvent was removed under reduced pressure. The residue was evaporated once with CS_2. The residual solid was crystallized twice from CS_2, then dried *in vacuo*; yield 6.72 g (82%), mp 86-88 °C. MS (FAB) *m/e* 275 (M + 1); IR (KBr) 2500-3200 (broad), 1720, 1707, 1701, 1418, 1317, 1240, 1188 cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.25 (s, 2, OH), 3.84 (q, 2, CH), 1.56 (d, 6, CH_3). *Anal.* Calcd for $C_6H_{10}O_4S_4$: C, 26.26; H, 3.67. Found: C, 26.18; H, 3.90.

Tetrathiobis-L-alanine Hydrochloride (4:7) (124). A stirred solution of L-cysteine (2.42 g, 20 mmol) in AcOH (900 mL) was treated with a 1 *M* solution of S_2Cl_2 in CH_2Cl_2 (10 mL, 10 mmol) under N_2. A white solid separated immediately. The mixture was stirred at 20-25 °C for 1 h, and the white solid was collected under N_2, then washed with Et_2O. The product was dried *in vacuo* overnight; yield 3.17 g (84%, mp 162-164 °C dec. MS (FAB) *m/e* 305 $(M + H)^+$; IR (KBr) 2400-3200 (broad), 1740, 1580, 1550, 1495, 1450, 1390, 1250, 1185 cm^{-1}; ^1H NMR, (CD_3OD) δ 4.45 (m, 2, CH), 3.50 (m, 4, CH_2S). *Anal.* Calcd for $C_6H_{12}N_2O_4S_4 \cdot 1.75HCl$: C, 19.57; H, 3.76; N, 7.61. Found: C, 1958; H, 3.84; N, 7.50.

Tetrathiobis-L-alanine diethyl ester dihydrochloride (125). A stirred suspension of L-cysteine ethyl ester hydrochloride (1.86 g, 10 mmol) in $CHCl_3$ (1.25 mL) was treated with a 1 *M* solution of S_2Cl_2 in CH_2Cl_2 (5 mL, 5 mmol). After the addition, most of the suspended solid dissolved. The reaction mixture was stirred at 20-25 °C for 5 h and was then chilled. The white solid that formed was collected, washed with $CHCl_3$, then Et_2O, and dried *in vacuo* for 18 h (P_2O_5); yield 2.12 g (98%), mp 143-145 °C. MS (FAB) *m/e* 361 $(M + H)^+$; IR (KBr) 2500-3100 (broad), 1751, 1743, 1512, 1293, 1279, 1132; ^1H NMR (CD_3OD) δ 4.48 (m, 2, CH), 4.35 (m, 4, CH_2), 3.57 (m, 4, CH_2-S), 1.36 (t, 6, CH_3). *Anal.* Calcd for $C_{10}H_{20}N_2O_4S_4 \cdot 2HCl \cdot 0.5H_2O$: C, 27.14; H, 5.24; N, 6.33. Found: C, 27.26; H, 5.03; N, 6.37.

Tetrathiobis-*N*-acetyl-L-alanine (126). A stirred solution of *N*-acetyl-L-cysteine (4.95 g, 30.3 mmol) in Me_2CO (100 mL) was treated with a 1 *M* solution of S_2Cl_2 in CH_2Cl_2 (15.15 mL, 15.2 mmol) at 20-25 °C. A semisolid separated. The mixture was stirred at 20-25 °C for 1 h then treated with Et_2O (200 mL). Stirring was continued for 30 min. The solid that formed was collected under N_2 then suspended in Me_2CO (60 mL), and the mixture was diluted with Et_2O (50 mL). The white solid was collected and dried *in vacuo*; yield 3.95 g (67%), mp 135-137 °C. MS (FAB) *m/e* 389 $(M + H)^+$; IR (KBr) 3401 (NH), 1722, 1623, 1425, 1375, 1345, 1296, 1217, 1175 cm^{-1}; ^1H NMR (CD_3OD) δ 4.78 (q, 2, CH), 3.55 (q, 4, CH_2), 3.40 (q, 4, CH_2), 200 (s, 6,

CH_3). *Anal.* Calcd for $C_{10}H_{16}N_2O_6S_4$: C, 30.91; H, 4.15; N, 7.21. Found: C, 31.01; H, 4.24; N, 7.22.

***N,N'*-[Tetrathiobis[1-[(carboxymethyl)carbamoyl]ethylene]]diglutamine Dihydrochloride (127).** Glutathione (3.07 g, 10 mmol) was dissolved in hot AcOH (1000 mL) and the solution was filtered to clarify. The solution was cooled to 20-25 °C and then treated with a 1 *M* solution of S_2Cl_2 in CH_2Cl_2 (5 mL, 5 mmol). A white solid separated. The mixture was stirred at 20-25°C for 30 min, and the white solid was collected, washed with AcOH and Et_2O. The product was dried *in vacuo* (P_2O_5): yield 3.2 g (80%), mp indefinite with decomp. MS (FAB) *m/e* 677 $(M + H)^+$; IR (KBr) 2700-3600 (broad), 1736, 1730, 1727, 1650, 1536, 1415, 1220 cm^{-1}. ^1H NMR (CD_3OD) δ 4.84 (m, 2, $CHCONH_2$), 4.04 (m, 2, CH-NH_2), 3.94 (s, 4, CH_2CO_2H), 3.52, 3.22 (2 m, 4, CH_2-S), 2.61 (t, 4, CH_2CONH), 2.21 (m, 4, CH_2CHNH_2). *Anal.* Calcd for $C_{20}H32N_6O_{12}S_4 \cdot 2HCl \cdot H_2O \cdot 0.5CH_3CO_2H$: C, 31.62; H, 4.80; N, 10.54; S, 16.08. Found: C, 31.65; H, 4.67; N, 10.57; S, 15.93.

3,3'-Tetrathiobis-DL-valine (128). DL-Penicillamine (2.98 g, 20 mmol) was dissolved in hot AcOH (250 mL), and then cooled to 20-25 °C. The stirred solution was treated with a 1 *M* solution of S_2Cl_2 in CH_2Cl_2 (10 mL, 10 mmol). A solid separated. The mixture was stirred at 20-25 °C for 30 min, then treated with Et_2O (500 mL). The mixture was stirred at 20-25 °C for 1 h and the solvent layer was removed by decantation. Stirring with Et_2O (500 mL) was repeated, and the solid was collected on a filter, washed with Et_2O, and dried *in vacuo* (P_2O_5); yield 3.46 g (80%), mp 165-167 °C. MS (FAB) *m/e* 361 $(M + H)^+$; IR (KBr) 3425 (NH), 2500-3200 (braod), 1745, 1585, 1500, 1456, 1220 cm^{-1}; ^1H NMR (CD_3OD) δ 4.99 (s, 4, NH_2), 4.15 (d, 2, $CHCO_2$), 1.67 (s, 6, CH_3), 1.55 (s, 6, CH_3). *Anal.* Calcd for $C_{10}H_{20}N_2O_4S_4 \cdot 2HCl$: C, 27.71; H, 5.12; N, 6.46. Found, C, 27.45; H, 5.14; N, 6.52.

2,2'-Tetrathio-bis-*N*-Acetylcysteamine Dihydrochloride (129). To a solution of *N*-acetylcysteamine (0.02 mol) in acetone (100 mL), sulfur monochloride (in CH_2Cl_2; 0.10 mL) was added dropwise under nitrogen atmosphere at room temperature. A white precipitate separated. The stirring was continued for 1 h. The product was then collected under nitrogen atmosphere, washed with acetone and diethyl ether, and finally dried under reduced pressure. Yield, 71%: mp 90-92 °C. *Anal.* Calcd for $C_8H_{16}O_2S_4N_2 \cdot 2HCl$. C, 25.73; H, 4.85; N, 7.50. Found C, 25.74; H, 4.49; N, 7.41. Mass $(M + H)^+$ 301.

***N,N''*-(Tetrathiodiethylene)-1,3-propanediamine Tetrahydrochloride (130).** 2-(3-

Aminopropylamino)ethanethiol dihydrochloride (10 mmol) (obtained *via* the following 3-step method was dissolved in hot acetic acid (250 mL) and then cooled to room temperature. The S_2Cl_2 (5 mmol) was added to the stirred solution. A white precipitate appeared. The stirring was continued for an additional hour. The precipitate was collected, washed with acetic acid and diethylether, and finally dried under reduced pressure. Yield 95%: mp 218-220 °C decomposed. *Anal.* Calcd for $C_{10}H_{28}S_4N_4 \cdot 4HCl$. C, 25.21, H, 6.35; N, 11.76. Found: C, 25.48; H, 6.46; N, 11.62. Mass $(M + H)^+$ 331.

Preparation of *N,N'*-(dithiodiethylene)-1,3-propane Diamine Tetrahydrochloride.

Step 1: *N*-(2-Bromoethyl)-1,3-propanediamine dihydrobromide. 2-(3-Aminopropyl)-aminoethanol (0.125 mole) was added dropwise to a stirred solution of 48% HBr (110 mL), with external cooling. The resulting solution was then distilled until the vapor temperature reached 122 °C. The solution was then refluxed for 64 h with slow distillation of the liquid until the total volume of distillate was ~80% (90 mL) of the original volume of 48% HBr. The cooled residue formed a semicrystalline mass that was stirred thoroughly with acetone, collected, and washed with ether. Treatment of a methanol solution of the precipitate with Norite, followed by re-precipitation *via* addition of ether gave a solid product, which was then recrystallized from the minimum volume of methanol to give the pure material (mp 205 °C (dec)), which was further recrystallized from ethanol.

Step 2. *S*-2-(3-Aminopropylamino)ethyl Dihydrogen phosphorothioate. Anhydrous Na_3SPO_3 (5.0 g) was added in several portions to rapidly stirred H_2O (25 mL) kept at 25 °C. A partial solution resulted containing some undissolved, well dispersed Na_3SPO_3. To the stirred suspension pure *N*-(2-bromoethyl)-1,3-propane diamine dihydrobromide (10.0 g) was added in portions. Additional water (5 mL) was used to rinse in any solid adhering to the glassware. Dissolution occurred readily, and the reaction was judged to be complete 1 h after it had turned clear. The solution was then poured in a thin stream into stirred methanol (500 mL). The white solid that separated was collected after 2 h, then washed with methanol, dissolved in H_2O, and reprecipitated by dropwise addition to stirred methanol (500 mL). The mixture was then kept in the refrigerator overnight. The solid was collected with the aid of methanol and dried to constant weight *in vacuo* over P_2O_5. The product was obtained in 90% yield. MS $(M - H)^-$, 213, $(M + H)^+$, 215.

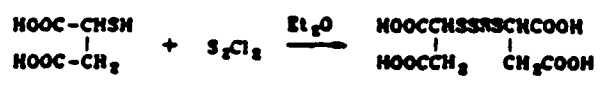
Step 3. Preparation of 2-(3-Aminopropylamino)ethanethiol Dihydrochloride. A solution of *S*-2-(3-

aminopropylamino)ethyl dihydrogen phosphorothioate (5.0 g) in 3 *N* HCl (50 mL) was heated at 90 °C for 10 min, and then evaporated to dryness under reduced pressure. The residual clear oil was dissolved in ethanol (25 mL) and dry HCl-EtOH solution (50 mL) was added. A white product precipitated. The solution was then refrigerated overnight, when additional white crystalline product separated. Et_2O (35 mL) was added, and the product was then collected, washed with Et_2O, and dried *in vacuo* (25-30 °C over P_2O_5: mp 192-194 °C (dec). (Reported 192-194 °C). MS $(M + H)^+$ 135.

2,2'-Tetrathio-bis-dimethylaminoethane Hydrochloride (131). Sulfur monochloride (0.10 mol) in CH_2Cl_2 was added to a solution of dimethylamino-ethanethiol (0.02 mole) in acetone (100 mL) at 20 °C. A white precipitate appeared. The stirring was continued for 1 h. The product was collected under nitrogen, washed with acetone and ether and finally dried under reduced pressure at room temperature. Yield 65%: mp 172-174 °C. *Anal.* Calcd for $C_8H_{20}N_2S_4HCl \cdot 1/2H_2O$. C, 30.21; H, 6.97; N, 8.83. Found: C, 30.47; H, 7.03; N, 8.57. MS (FAB) *m/e* 273 $(M + H)^+$.

2,2'-Tetrathio-bis-aminoethane Dihydrochloride (132). 2-Aminoethanethiol (0.03 mol) was dissolved in 100 mL of acetic acid. Sulfur monochloride in CH_2Cl_2 (0.12 mol) was then added dropwise under N_2 atmosphere to the stirred solution to give a white precipitate. The stirring was continued for 1/2 h at room temperature. The white solid product was collected under nitrogen, washed with acetic acid and then with diethyl ether and dried under reduced pressure over P_2O_5 at room temperature. Yield: 58%, mp 155-157 °C. *Anal.* Calcd for $C_4H_{12}N_2S_2 \cdot 2HCl$. C, 16.60; H, 4.88; N, 9.68. Found: C, 16.85; H, 4.96; N, 9.82. MS 217 $(M + H)^+$.

Succinic Acid, Tetrathio-bi (133).



A solution of mercaptosuccinic acid (6 g, 40 mmol) in 300 mL ether was treated with S_2Cl_2 (20 mL, 20 mmol-1 *M* solution in CH_2Cl_2) with good stirring. After ~45 min a precipitate began to form. The reaction was stirred 1 h longer, the product was collected, washed with ether, and dried *in vacuo* over phosphorus pentoxide; yield: 2.5 g (35%). Mp 188-19[illegible] °C; MS (FAB) *m/e* 363 $(M + H)^+$; IR 1694, 1412, 1292, 1235, 1185, 935, 920 cm^{-1}; ^1H NMR (CD_3OD) δ 4.04 (q, 1, C*H*), 3.11, 2.88 (2dd, 2, CH_2). *Anal.* Calcd

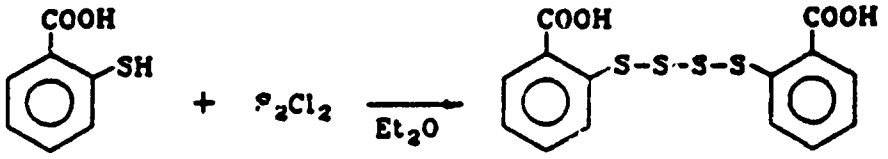
for $C_8H_{10}O_8S_4$: C, 26.51; H, 2.78. Found C, 26.84; H, 2.55.

4,4'-Tetrathio-*bis*-benzeneamine, Dihydrochloride (134).

SoRI 8599.

A solution of sulfur monochloride (1 *M* in dichloromethane, 7.0 mL) was added slowly to a stirred solution of 4-aminothiophenol (1.98 g) in 100 mL acetone at 20 °C. A precipitate immediately appeared after the addition. Stirring was continued for 30 min. The precipitate was filtered under nitrogen and washed first with acetone then with diethyl ether, then dried under reduced pressure over P_2O_5, mp 64-66 °C (decomposed). Yield 84%. *Anal.* Calcd for $C_{12}H_{12}N_2S_4 2HCl \cdot H_2O$: C, 35.73; H, 4.00; N, 6.94. Found: C, 35.68; H, 3.98; N, 6.6. MS $(M + H)^+$ 312.

2,2'-Tetrathio-*bis*-benzoic Acid (135).



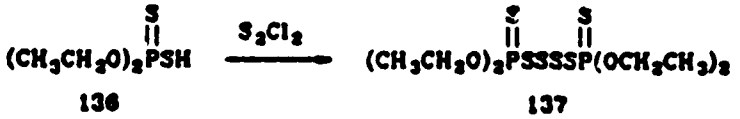
SoRI 8624.

2-Thiosalicyclic acid (3 g, 19.5 mmol) was suspended in 200 mL Et_2O and S_2Cl_2 (9.7 mL, 9.7 mmol, 1 *M* in CH_2Cl_2) was added quickly (~30 sec) with good stirring. The product rapidly began to precipitate. The mixture was stirred 30 min and then product was collected, washed with Et_2O, and dried. Yield, 3.1 g (86%) (lt. yellow powder); IR 1672, 1586, 1560, 1463, 1435, 1416, 1310, 1288. 740 cm^{-1}. *Anal.* Calcd for $C_{14}H_{10}O_4S_4$: C, 45.39; H, 2.72. Found: C, 45.38; H, 2.70.

B. TETRASULFIDES DERIVED FROM PHOSPHONATES AND THIOCARBAMATES.

1. O,O,O',O'-Tetraethyl Tetrathiobisphosphonothioate

The title compound 137 was prepared from O,O'-diethyl dithiophosphate (136) and S_2Cl_2 in Et_2O as in a reported procedure.[21]



136 137

2. Attempted Conversions of *N,N*-Dialkyl Dithiocarbamates to Tetrasulfide Derivatives

Attempts to convert *N,N*-diethyl and *N,N*-dibenzyl dithiocarbamates to the tetrasulfide derivatives of structural type 138 by treatment with S_2Cl_2 in CH_2Cl_2 were abandoned when no pure desired product could be obtained from either starting compound. Only crude and malodorous mixtures of decomposition products resulted.

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EXPERIMENTAL SECTION FOR PART VI.3.

Tetraethyl Tetrathiobisphosphonothioate (137). A stirred solution of O,O,-diethyl dithiophosphate 1.86 g (10 mmol) in anhydrous Et_2O (50 mL) was treated with a solution of S_2Cl_2 in CH_2Cl_2 (5 mL of 1 *M*). The reaction solution was stirred at 20-25 °C for 1 h, and then the solvent was removed under reduced pressure. The residual yellow oil was dried *in vacuo*; yield 1.77 g (82%). MS (FAB) *m/e* 435 (M + 1); IR (KBr) 2982, 1389, 1161, 1100, 1009, 970, 830, 801, 645, 503, 471, 355 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.32, 4.18 (2 m, 8, OCH_2), 1.42 (apparent t, 12, $-CH_3$). *Anal.* Calcd for $C_8H_{20}O_4P_2S_6$: C, 22.11; H, 4.64. Found: C, 22.44; H, 4.74.

C. DISULFIDES AND RELATED COMPOUNDS.

Disulfide 143 and thiomethyl compound 140 were prepared according to methods shown below and were submitted for testing this period. Both compounds were already known from the patent literature.[20] Physical data is reported in Table 14.

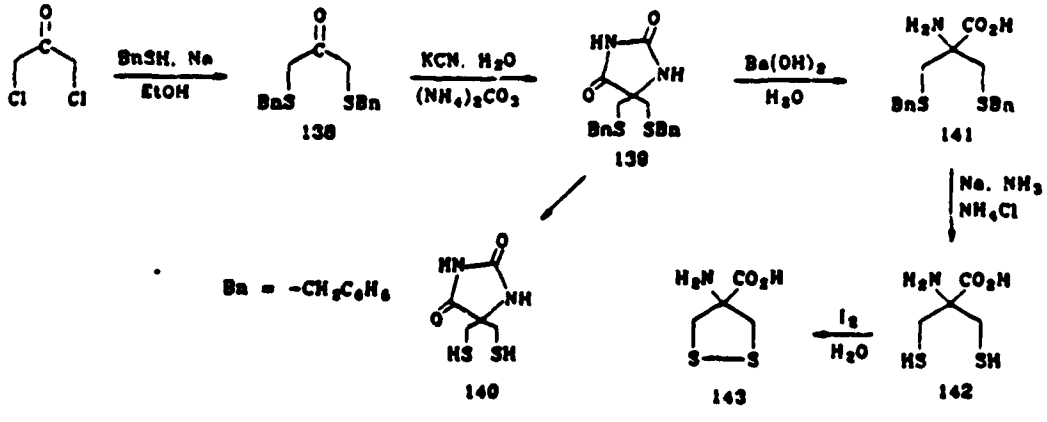


TABLE 14. DISULFIDES AND RELATED COMPOUNDS.						
				Elemental Analyses Calcd Found		
Structure No.	Yield, %	Mp, °C	Molecular Formula (Formula Wt.)	%C	%H	%N
143	45	192-194	$C_8H_8N_2O_2S_2$ (192.25)	31.25 31.28	4.17 4.17	14.58 14.44
140	40	175-183	$C_4H_7NO_2S_2 \cdot H_2O$ (183.23)	26.23 26.13	4.92 4.90	7.65 7.51

EXPERIMENTAL SECTION FOR PART VI.C.

5,5-Bis(thiomethyl)hydantoin (140) in Three Steps. Step 1. 1,3-Bis-(benzylthio)-acetone (138). Na metal (23.0 g, 1.00 mol) was added in small pieces to a well-stirred solution of benzyl mercaptan (118 mL, 1 mol) in 400 mL absolute ethanol, which was cooled in an ice bath during the addition of Na. A solution of 1,3-dichloroacetone (63.5 g, 0.5 mol) in 100 mL absolute ethanol was added dropwise during a 2 h period with continued stirring and cooling. After the addition was completed, the reaction was allowed to stir at 20-25 °C overnight (18 h). The solvent was evaporated *in vacuo*, and the residue was taken up in 400 mL ether and filtered from inorganic matter. The filtrate was washed twice with 100-mL portions of H_2O, dried over $MgSO_4$, then evaporated *in vacuo* to a dark viscous oil (104.7 g). **Step 2. 5,5-Bis(benzylthiomethyl)hydantoin (139).** The residue from Step 1 in 1050 mL absolute ethanol was warmed to 60-70 °C with stirring in an oil bath. A solution of potassium cyanide (35 g) in 350 mL H_2O was added followed by 210 g of solid ammonium carbonate. Stirring was continued at 60-70 °C for 24 h. Upon cooling a brown solid separated and was collected by filtration, then washed with ethanol and H_2O to give 77 g of light beige solid. **Step 3. 5,5-Bis(thiomethyl)hydantoin (140).** A portion (4.0 g) of the solid from Step 2 was dissolved in 100 mL of liquid NH_3. The solution was treated with small portions of Na with vigorous stirring until the mixture developed permanent blue color. The blue color was discharged by the addition of ammonium chloride, then more ammonium chloride was added (a quantity equivalent to the Na used). The ammonia was allowed to evaporate at 20-25 °C overnight under a slow stream of N_2 leaving a solid residue. Column chromatography (using 60-200 mesh silica gel and elution with $CHCl_3$-MeOH, 95:5) was used to obtain pure

140, mp, 198-202 °C. *Anal.* Calcd for $C_9H_8N_2O_2S_2$: C, 31.25; H, 4.17; N, 14.58. Found: C, 31.10; H, 4.02; N, 14.40. MS (EI) *m/z* 92 (M^+). ^1H NMR (Me_2SO-d_6) δ 10.84 (br s, 1, NH-3), 7.78 (s, 1, NH-1), 2.80 (d, 2, J = 14, CH_2SH), 2.71 (d, 2, J = 14, CH_2SH), 2.36 (br s, 2, SH).

4-Amino-1,2-dithiolane-4-carboxylic Acid (143) in Three Steps from 5,5-Bis(benzylthiomethyl)hydantoin (139). Step 1. 2,2-Bis(benzylthiomethyl)glycine (141). Crude 5,5-*bis*(benzylthiomethyl)hydantoin 139 (70 g) in 1.75 L of H_2O containing 215 g of dried $Ba(OH)_2$ was refluxed for 12 days. The reaction mixture was cooled and made strongly acidic with concentrated hydrochloric acid to dissolve suspended barium salts. The undissolved solid was collected by filtration and washed with H_2O. The solid was then added to ethanol and the mixture was stirred 20 min. before the insoluble was collected giving 43.42 g of product. **Step 2. 2,2-Bis(thiomethyl)glycine (142).** A solution of 41.25 g (119 mmol) of the product from Step 1 in 910 mL anhydrous NH_3 was treated with Na metal in small pieces with vigorous stirring until the mixture developed a permanent blue color. The blue color was discharged by the addition of a small amount of ammonium chloride. More ammonium chloride, equivalent to the quantity of Na used, was then added. The ammonia was allowed to evaporate at 20-25 °C overnight under a slow stream of N_2. The residue was taken up in 800 mL H_2O, and the pH of the solution was adjusted to 6 by the addition of dilute HCl. The solution was then extracted with 300 mL Et_2O. The ethereal phase was discarded, and the aqueous phase containing the product was used in Step 3 which follows. **Step 3. 4-Amino-1,2-dithiolane-4-carboxylic Acid (143).** The aqueous phase from Step 2 was added slowly to stirred 2 *N* I_2-KI solution. The excess was destroyed with aqueous 10% $NaHSO_3$. The solution was extracted with 300 mL Et_2O, and the aqueous phase was neutralized with concentrated NH_4OH. The neutral solution was filtered free of undissolved material, and the filtrate was concentrated *in vacuo* to 500 mL. A yellow solid separated out and was filtered off, then washed with H_2O to give 25 as a monohydrate, mp 165-173 °C dec. *Anal.* Calcd for $C_4H_7NO_2S \cdot H_2O$: C, 26.23; H, 4.92; N, 7.65. Found: C, 26.24; H, 4.90; N, 7.79. MS (EI), *m/z* 183 (M^+). ^1H NMR (Me_2SO-d_6) δ 7.88 (br s, 1, NH_2), 3.50 and 3.32 (two d, 4, due to nonequivalent CH_2 groups).

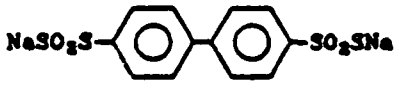
D. THIOSULFONATES.

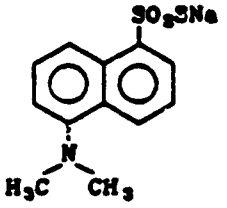
We also attempted to synthesize some thiosulfonate compounds which could detoxify cyanide through interaction with the mammalian sulfurtransferase pathway, as already mentioned. In particular, these

compounds would act as substrates in rhodanese-promoted reactions.[25] We submitted the ten novel agents whose structures are given below.

RSO_2SNa

144: R = CH_3
145: R = CH_3CH_2
146: R = $(CH_3)_2CH$
147: R = Ph
148: R = 4-MePh
149: R = 4-BnPh
150: R = 4-t-BuPh
151: R = β-naphthyl

152 

153 

These compounds were prepared by treatment of the corresponding sulfonyl chlorides with sodium sulfide as described in the literature.[25] In addition to the submitted compounds, several thiosulfonates were prepared as intractable mixtures which could not be purified. Table 15 summarizes the properties of the submitted thiosulfonates.

EXPERIMENTAL SECTION FOR PART VI.D.

Sodium Methanesulfonothioate (144) and analogous compounds 145-153 were prepared by a reported general procedure[25]. The procedure for the preparation of 147 is given as a typical example. Benzenesulfonyl chloride (10 g, 57 mmol) was added dropwise to a stirred solution of $Na_2S{\cdot}9H_2O$ (13.6 g, 57 mmol) in H_2O (50 mL) kept at 95-100 °C. The stirred mixture was then refluxed overnight (about 16 h). The resulting clear solution was evaporated to dryness (1 mm, rotary evaporator, bath 20-25 °C). The dry residue was extracted with hot EtOH and was recrystallized twice from EtOH.

E. THIOSULFATES.

The susceptibility of thiosulfates to nucleophilic attack inspired our synthesis of a number of thiosulfate-containing compounds by following precedented methods.[45,30]. Compounds 154-162 were prepared by reacting sodium thiosulfate with the appropriate dihaloalkanes in EtOH-H_2O. Compounds 163-165 were prepared by bromoalkylamine with magnesium thiosulfate. The *S*-sulfo derivatives of cysteine (166), penicillamine (167, and glycine 176), and compound 168 were synthesized by treatment of the parent thiol with chlorosulfonic acid. The barium salt of *S*-sulfoglutathione was similarly prepared, and after purification was converted to the sodium salt for efficacy testing. Compounds 170-175 and 177 were made by reacting

TABLE 15. THIOSULFONATES.

Structure No.	Yield, %	Mp, °C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd / Found %C	%H	%N	%S	Mass (FAB) cation, anion or MH^+
144	74	256-260	$CH_3O_2S_2Na \cdot H_2O$ (152.16)	7.89 7.78	3.31 3.27			23, 111
145	66	280-281	$C_2H_5O_2S_2Na$ (148.18)	16.21 16.03	3.40 3.58			23, 125
146	52	310-315	$C_3H_7O_2S_2Na$ (162.20)	22.21 22.31	4.35 4.30			23, 139
147	55	285-286	$C_6H_5O_2S_2Na$ (196.22)	36.73 36.26	2.57 2.55			23, 173
148	86	298-300	$C_7H_7O_2S_2Na$ (210.25)	39.99 39.45	3.35 3.34			23, 187
149	69	>350	$C_6H_4BrO_2S_2Na$ (275.14)	26.19 25.94	1.46 1.52			23, 251
150	78	325-330	$C_{10}H_{13}O_2S_2Na$ (252.33)	47.60 47.49	5.19 5.18		25.41 25.41	2M - Na, 449 2M + Na, 495
151	60	314-316	$C_{10}H_7O_2S_2Na$ (246.25)	48.76 48.71	2.86 2.76			23, 223
152	77	>300	$C_{12}H_8S_4O_4Na_2$	36.93 36.64	2.07 2.03			390-Na, 367 390-2Na, 345
153	26	236-238	$C_{12}H_{12}NO_2S_2Na$	44.81 49.15	4.18 4.16	4.84 4.73		M + H, 290

the corresponding chloroamidine, generated *in situ*, with magnesium thiosulfate. The structures of these sulfane sulfur donors, and of additional examples subsequently submitted, are summarized in the diagrams below, and their physical data follow in Table 16.

$^{-}O_3SS(CH_2)_nSSO_3^{-}$

154: n = 2

155: n = 3

156: n = 4

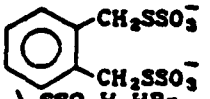
157: n = 5

158: n = 6

$RO_2C(CH_2)_nSSO_3^{-}$

159: n = 4, R = CH_3

160: n = 7, R = H



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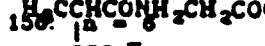


159

177

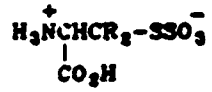
161

$R'_2\overset{+}{N}H(CH_2)_nSSO_3^{-}$

163: n = 2, R' = H

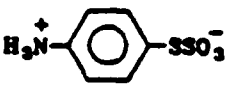
164: n = 2, R' = Me

165: n = 3, R' = H

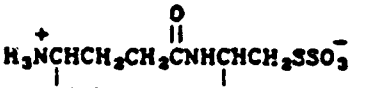


166: R = H

167: R = CH_3



168



169

170: R = Me, R' = H

171: R = R' = Me

172: R = Et, R' = H

173: R = i-Pr, R' = H

174: R = Bn, R' = H

175: R = 2-adamantyl, R' = H

TABLE 16. THIOSULFATES.

Structure No.	Yield, %	Mp, °C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd Found %C	%H	%N
154	42	260-265	$C_2H_4O_6S_4Na_2$ (298.28)	8.05 7.44	8.00 1.31	
155	64	310-315	$C_3H_6O_6S_4Na_2 \cdot H_2O$ (330.32)	10.91 10.56	2.44 2.39	
156	52	280-284	$C_6H_{14}O_6S_4Na_2 \cdot H_2O$ (374.42)	19.36 18.95	3.78 3.92	
157	68	245-250	$C_8H_{16}O_6S_4Na_2 \cdot H_2O$ (400.45)	24.00 24.13	4.53 4.59	
158	70	172-175	$C_{10}H_{20}O_6S_4Na_2 \cdot H_2O$ (428.51)	28.03 5.17	28.33 5.18	
159	57	101-102	$C_6H_{11}O_3S_2Na \cdot H_2O$ (268.29)	26.86 26.19	4.88 4.33	
160	36	140-150	$C_6H_{15}O_5S_2Na \cdot H_2O$ (296.34)	32.43 32.46	5.78 5.38	
161	62	138-140	$C_3H_4Na_2S_4O_7 \cdot H_2O$ (344.33)	10.46 10.34	1.75 1.69	
162	30	195-198	$C_8H_8Na_2S_4O_6 \cdot 1.5H_2O$ (317.42)	23.94 24.05	2.76 2.63	
163	87	194-196 (lit. mp 195-196)	$C_2H_7NO_3S_2$ (157.22)	15.28 15.23	4.49 4.40	8.91 8.75
164	42	160-162	$C_4H_{11}S_2NO_3$ (185.26)	24.96 25.00	6.17 6.17	7.27 7.03
165	60	184-186 (lit. mp 189-196)	$C_3H_9NO_3S_2$ (171.25)	21.04 21.07	5.30 5.33	8.18 7.82
166	90	204-205 (lit. mp 204-205)	$C_3H_7NO_5S_2 \cdot H_2O$ (219.22)	16.43 16.73	4.13 4.33	6.39 6.16
167	71	202-203 (lit. mp [illegible])	$C_5H_{11}NO_5S_2$ (229.28)	26.20 26.19	4.84 4.84	6.10 5.98
168	90	214-216 (lit. mp 254-255)	$C_6H_7NO_3S_2$ (205.26)	35.10 35.18	3.43 3.45	6.82 6.66

TABLE 16. (Continued)

Structure No.	% Yield	Mp, °C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd / Found %C	%H	%N
169	62		$C_{10}H_{18}Na_2S_2N_3O_9 \cdot 2H_2O$ (449.38)	25.69 25.58	4.09 3.77	8.99 8.88
170	48	154-156	$C_3H_8N_2O_3S_2$ (185.25)	19.56 19.51	4.38 4.33	15.21 15.02
171	74	174-175 (174)	$C_4H_{10}N_2O_3S_2$ (198.27)	24.23 24.33	5.08 5.02	14.13 14.03
172	89	144-145 (164)	$C_4H_{10}N_2O_3S_2$ (198.27)	24.23 24.30	5.08 5.14	14.13 14.03
173	36	154-156 149-150	$C_5H_{12}N_2O_3S_2 \cdot H_2O$ (244.30)	28.29 28.27	5.70 5.75	13.19 13.08
174	78	154-156	$C_9H_{12}N_2O_3S_2$ (260.34)	41.52 41.69	4.65 5.04	10.76 10.22
175	65	185-187	$C_{12}H_{20}N_2O_3S_2$ (304.00)	47.34 47.43	6.62 6.71	9.20 9.15
176	76	145-146	$C_5H_9NO_6S_2$ (243.26)	24.68 24.69	3.72 3.90	5.75 5.66
177	65	138-142	$C_8H_{14}N_2O_3S_2 \cdot HBr$ (295.22)	20.34 20.38	5.46 5.37	9.47 9.28

EXPERIMENTAL SECTION FOR PART VI.E.

Disodium *S,S'*-1,2-Ethanediyl Bis(thiosulfate) (154) and Homologs 155-158. The α,ω-dibromoalkane and two molar equivalents of $Na_2S_2O_3 \cdot 3H_2O$ were dissolved in EtOH-H_2O (1:1 by volume, 50 mL per 0.01 mol of $Na_2S_2O_3 \cdot H_2O$). The solution was refluxed 2 h, cooled, and evaporated to dryness. The residue was recrystallized from EtOH (9:1 by volume).

Sodium *S*-[ω-(Methoxycarbonyl)butyl] Thiosulfate (159) and Sodium *S*-(7-Carboxyheptyl) Thiosulfate (160). Equimolar amounts of the appropriate ω-substituted bromo compounds and $Na_2S_2O_3 \cdot 5H_2O$ in H_2O containing sufficient EtOH to produce a clear solution was refluxed 2 h, cooled, and evaporated *in vacuo*. The residues were recrystallized from H_2O by addition of EtOH three or four times or until the precipitated solid was free of NaBr. Products were dried *in vacuo*.

Synthesis of Bifunctional Bunte Salts (161, 162). A mixture of dichloroacetone or α,α'-dibromo-*O*-xylene (0.1 mol) and sodium thiosulfate (0.2 mol) in 50% alcohol (60 mL) was refluxed for 10 min - 2 hr. Solvent was removed to dryness and 90% alcohol added, followed by warming to 50 °C. On cooling the product separated and after filtration was crystallized 3-4 times from hot aqueous ethanol (90%).

Thiosulfuric acid, 2 oxo-*S,S*-1,3-propanediyl ester, disodium salt (161). Yield 62%; mp 138-40 °C. *Anal.* Calcd for $C_3H_4O_7S_4Na_2 1H_2O$: C, 10.46; H, 1.75. Found C, 10.34; H, 1.69. MS (neg FAB) *m/e* 303 (M - Na).

Thiosulfuric acid, *S,S'*-(*O*-phenylene)diylester, disodium salt (162). Yield 39%, mp, 195-198 °C. *Anal.* Calcd for $C_8H_8O_6S_4Na_2 1.5H_2O$: C, 23.94; H, 2.76. Found: C, 24.05; H, 2.63. MS (neg FAB) *m/e* 351 $(M - Na)^-$, 397 $(M + Na)^+$.

***S*-(2-Amiaoethyl)-Thiosulfuric Acid (163) and *S*-(3-Aminopropyl)-Thiosulfuric Acid (165).** A solution of equimolar amounts of 2-bromoethylamine hydrobromide (for 163) or 3-bromopropylamine hydrobromide (for 165) with MgS_2O_3-$6H_2O$ in MeOH (1 mL per mmol of MgS_2O_3-$6H_2O$) was kept at 60 °C for 1 h. The cooled solution deposited the product 163 or 165. Results are included in Table 16.

2-Dimethylaminoethanethiosulfuric Acid (164). A mixture of 2-dimethylaminoethylchloride hydrochloride and magnesium thiosulfate (0.1 mol) in methanol (2.5 mL) was heated on a water bath at 60-65 °C for 2 h. Methanol was then removed under reduced pressure, leaving a viscous product. Aqueous ethanol (95%) was added to precipitate the solid product, which was recrystallized from 95% ethanol 3-4 times until $MgCl_2$ free. Yield 42%, mp 160-162 °C. *Anal.* Calcd for: C, 24.96; H, 6.17; N, 7.27. Found: C, 25.0, H, 6.17; N, 7.03. MS (neg FAB) *m/e* 184 $(M - H)^-$.

***S*-Sulfocysteine (166), *S*-Sulfopenicillamine, and *S*-Sulfopenicillamine (167), and *S*-4-Aminophenyl Thiosulfuric Acid (168).** These three candidates were prepared by treatment of the corresponding thiols with $ClSO_3H$ in glacial AcOH as described by Tanaka *et al.*[30] The reported procedures proved to be readily reproduced.

Preparation of Glycine, *N*-(*N*-L-γ-glutamyl-*S*-Sulfo-L-cystinyl), Disodium Salt, Dihydrate (169) (Sodium Glutathionate).

Step 1. Barium Glutathionate. Glutathione (6.4 mmol) was added to a reaction mixture of sodium sulfite (26.0 mmol) in 98 mL of a 0.05 M $CuSO_4$ solution adjusted to pH 10 with concentrated ammonia. The

reaction was stirred for 2 hr at room temperature and then the mixture was kept in the refrigerator overnight. The solution (~40 mL) was concentrated on a rotary evaporator and passed through a column of Dowex 50 W (H^+ form, 100-200 mesh; 2 x 20 cm) with water as eluant. The eluate containing $GSSO_3H$ was again concentrated, treated with 8.0 g of barium acetate, and dissolved in 25 mL of water. The resulting precipitate was removed by centrifugation and the barium salt of $GSSO_3H$ was precipitated from the supernatant by the addition of 5 volumes of 95% ethanol. The barium salt was reprecipitated 4 times with ethanol and was then dried over P_2O_5 under vacuum. Yield 62%. *Anal.* Calcd for $C_{10}H_{15}N_3O_9S_2Ba \cdot 2H_2O$: C, 21.49; H, 3.42; N, 7.51. Found: C, 21.51; H, 3.29; N, 7.02. MS (FAB) *m/e* 524 $(M + H)^+$, 522 $(M - H)^-$.

Step 2. Sodium Glutathionate. Barium glutathionate (2.50 g) was dissolved in 20 mL of water and sodium sulfate (0.634 g) was added at room temperature barium sulfate was removed by filtration and the filtrate freeze dried and stored in the freezer. (Yield 100%.) *Anal.* Calcd for $C_{10}H_{15}N_3O_9S_2Na_2 \cdot 2H_2O$: C, 25.69; H, 4.09; N, 8.99. Found: C, 25.58; H, 3.77; N, 8.88. MS (FAB) *m/e* 430 $(M - H)^-$, 432 $(M + H)^+$, 408 (M - Na).

Synthesis of α-Amidinium thiosulfate S (Bunte Salts) (170-174).

(a) α-Chloroamidine Hydrochlorides.

α-Chloropropionitrile (0.1 mol) was added dropwise to a stirred solution of 0.01 mol of sodium methoxide in dry methanol (100 mL) at 25 °C. After one hour of stirring, the amine hydrochlorides (0.11 mol) were added and the reaction mixture was stirred for 16-24 h at 25 °C. The mixture was filtered to remove all solids and the solvent was removed from the filtrate. The resulting residue was triturated with ether and the solid products were carried further without purification.

(b) α-Amidiniumthiosulfates.

These were prepared for the corresponding α-chloroamidine hydrochlorides. α-Chloroamidine, dissolved in 25-30 mL of water, was treated with sodium thiosulfate and refluxed 1 hr. The reaction mixture was allowed to cool to room temperature, after which the compounds separated and were removed by filtration. Purification by recrystallization from ethanol (3 times) was followed by drying under reduced pressure.

***S*-[*N*-(2-Adamantyl)amidino]methyl Hydrogen Thiosulfate (175).** A solution of chloroacetonitrile (0.01 mol) in methanol (25 mL) was added to a stirred solution of sodium methoxide obtained from 10 mmol

(0.23 g) of Na in methanol (50 mL) at 25 °C. A 30 min time was allowed for the reaction. Then a solution of 2-adamantanamine hydrochloride (0.8 mol) in methanol was added. A reddish brown color developed after 45 min, then solid magnesium thiosulfate (0.8 mol) was added in one portion with stirring. The resulting solution was stirred at room temperature for 3 h. The solid product separated, which was collected, washed successively with ethanol and diethyl ether, and finally dried under reduced pressure to give the pure product. Yield 65%, mp 185-186 °C. Decomposed (Lit. 185-187 °C). *Anal.* Calcd for $C_{12}H_{20}N_2O_3S_2$: C, 47.34; H, 6.62; N, 9.20. Found C, 47.43; H, 6.71; N, 9.15. MS (FAB) *m/e* 305 $(M + H)^+$, 303 $(M - H)^-$.

***N*-[1-Oxo-2-(sulfothio)propyl]glycine (176).** Chlorosulfonic acid (0.021 mole) was added slowly to a stirred solution of *N*-(2-mercaptopropionyl)glycine) in 100 mL of acetic acid at room temperature (25 °C). The white precipitate appeared, and stirring was continued for 1/2 h. The precipitate was collected under nitrogen atmosphere, which was washed with acetic acid and then ether, and finally dried over P_2O_5 under reduced pressure. Yield 76%: mp 145-146 °C. *Anal.* Calcd for $C_5H_9NO_6S_2$: C, 24.68; H, 3.72; N, 5.75. Found: C, 24.20; H, 3.81; N, 5.61. MS (neg FAB) *m/e* 243 $(M - H)^-$.

***S*-2-(3-Aminopropylamino)ethyl Hydrogen Thiosulfate Hydrobromide (177).**

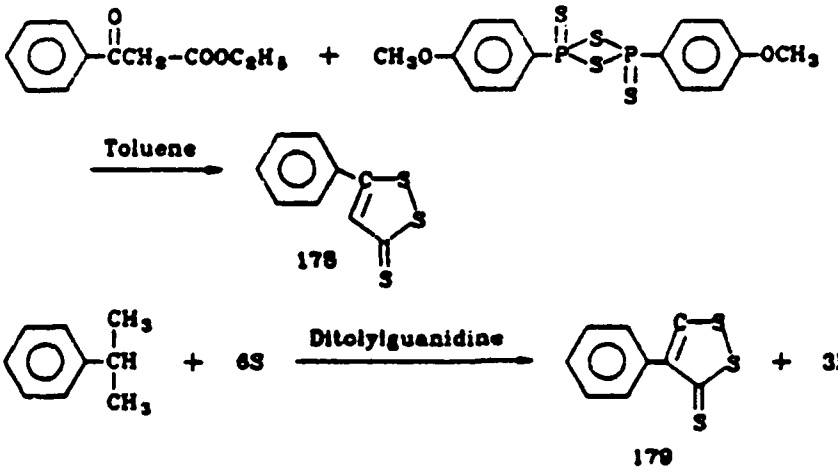
SoRI 8598.

Equimolar amounts of magnesium thiosulfate and sodium acetate (0.1 mole) in methanol (25 mL) were added to a solution of *N*-(2-bromoethyl)-1,3-propanediamine dihydrobromide (0.1 mole) in methanol. The resulting mixture was heated for 2 h at 60 °C. The solution was then concentrated to ~20 mL and kept in the refrigerator for 6-7 days. A white solid product crystallized which was washed first with 95% alcohol and then methanol, and finally dried under reduced pressure. Yield 65%: mp 138-142 °C. *Anal.* Calcd for $C_5H_{14}N_2S_2O_3HBr$: C, 20.34; H, 5.46; N, 9.47. Found: C, 20.38; H, 5.37; N, 9.28. MS (FAB) *m/e* 215 $(M + H)^+$, 213 $(M - H)^-$.

F. 3-*H*-1,2-DITHIOLE-3-THIONES.

Two routes were investigated for the preparation of the title compounds as shown below. The first method the reaction of ethylbenzoylacetate with elemental sulfur and Lawesson's reagent consistently gave low yields and therefore, a preparation treating cumene (isopropylbenzene) with elemental sulfur and ditolylguanidine[5] was also tried. Unfortunately, the second approach was also not very successful, and

therefore, only two examples of this series structures 178 and 179 were submitted.



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EXPERIMENTAL SECTION FOR PART VI.F.

Preparation of Dithiolethiones 178 and 179.

(a) 0.005 Mole of ethyl benzoylacetate, 0.012 mol of Lawesson's reagent, and 0.01 mol of elemental sulfur in 10 mL anhydrous toluene were kept at 110 °C for 10 hrs. After cooling to room temperature the mixture was placed on a silica gel column and the toluene was eluted with petroleum ether/ether (95/5). The eluent was changed to petroleum ether/ether (70/30) and the 1,2-dithiole-3-thione was isolated.[4] MS and CHN analyses confirmed the structure. Yields were low in each attempt.

(b) 0.1 Mole of cumene, 0.15 mol of sulfur, and 0.04 g of ditolylguanidine were refluxed for 21 hrs. The mixture was then kept at 5 °C for 2 hrs. to allow the 1,2-dithiole-3-thione to crystallize.[5]

Reaction of 3-oxoesters with *p*-methoxyphenylthionophosphine sulfide. Ethylbenzoylacetate (0.005 mol), 0.012 mol of Lawesson reagent, and sulfur (0.01 mol) were taken up in 10 mL of anhydrous toluene and heated at 110 °C for 10 h. After cooling to room temperature, the mixture was placed on a silica gel column and the toluene was eluted with ether/light pet. ether (10:90). On a renewed elution with ether/light pet. ether (30:70), the 3*H*-1,2-dithiole-3-thiones were isolated, and identified by mp, MS, and elemental analyses, mp, 125-126 °C, reported, 126 °C. MS (FAB) *m/e* 211 $(M + H)^+$. *Anal.* Calcd for $C_9H_6S_3$. C, 51.43; H, 2.86. Found: C, 51.42; H, 2.74.

TABLE 17. 3-*H*-1,2-DITHIOLE-3-THIONES						
Structure No.	Yield, %	Mp, °C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd Found		
				%C	%H	%N
30	Unavailable	125-126 (lit. 126)	$C_9H_6S_3$ (210.33)	51.43 51.42	2.86 2.74	-- --
57	71	118-121	$C_9H_6S_3$ (210.33)	51.43 51.64	2.86 2.86	-- --

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TABLE 18. COMPOUNDS SUBMITTED FOR TESTING AS ANTICYANIDE AGENTS.
CONTRACT NO. DAMD17-90-C-0011
9 MARCH 1990 – 8 August 1993
(STRUCTURES SHOWN IN TABLE 20)

WR No.	WR Bottle No.	SoRI No.	Sample No.	Description in Quarterly Progress Report No., (pages)
268785	BM 05503	8602	F828-9-2	1, (6-7)
268786	BM 05512	7603	F828-15-1	1, (6-7)
268787	BM 05521	7624	F590-147-3	1, (3-4)
268788	BM 05530	7625	F590-125-1	1, (3-4)
268789	BM 05549	7626	F590-131-4	1, (3-4)
268790	BM 05558	7627	F590-141-3	1, (3-4)
268827	BM 06000	7634	F828-23-1	2, (15-17)
268828	BM 06019	7635	F828-19-1	2, (15-17)
268829	BM 06028	7636	F828-29-1	2, (15-17)
268830	BM 06037	7637	F828-21-1	2, (15-17)
268831	BM 06046	7638	F828-31-1	2, (15-17)
268832	BM 06055	7656	F828-35-1	2, (15-17)
268833	BM 06064	7667	F590-143-3	2, (13-15)
268834	BM 06073	7668	F590-133-3	2, (13-15)
268835	BM 06082	7669	F590-151-1	2, (13-15)
268836	BM 06091	7670	F590-139-4	2, (13-15)
268837	BM 06108	7671	F866-47-1	2, (6-9)
268838	BM 06117	7672	F866-23-2	2, (6-9)
268839	BM 06126	7673	F866-9-1	2, (6-9)
269940	BM 06135	7674	F866-49-1	2, (6-9)
268841	BM 06144	7675	F866-25-1	2, (6-9)
268820	BM 06153	7676	F866-51-1	2, (6-9)
257838	BM 06162	7677	F866-19-1	2, (6-9)
268844	BM 06171	7678	F866-59-1	2, (6-9)
268798	BM 06180	7679	F866-31-1	2, (6-9)
268845	BM 06199	7680	F866-61-1	2, (6-9)
268846	BM 06206	7685	F828-47-1	2, (17)

TABLE 18. (Continued)

WR No.	WR Bottle No.	SoRI No.	Sample No.	Description in Quarterly Progress Report No., (pages)
268911AA	BM 07141	7703	F850-25-2	3, (11-12)
268912AA	BM 07150	7704	F850-35-2	3, (11-12)
268913AA	BM 07169	7705	F850-41-1	3, (11-12)
268914AA	BM 07178	7720	F866-99-1	3, (5-8)
268915AA	BM 07187	7721	F866-101-1	3, (5-8)
268916AA	BM 07194	7722	F866-83-1	3, (5-8)
268917AA	BM 07203	7723	F866-115-1	3, (5-6)
268918AA	BM 07212	7724	F866-117-1	3, (5-6)
268919AA	BM 07221	7725	F866-63-1	2,(7-10)
268920AA	BM 07230	7726	F866-73-1	2, (7-10)
268921AA	BM 07249	7727	F866-93-1	3, (5)
268922AA	BM 07258	7728	F866-75-1	2, (7-10)
268923AA	BM 07267	7730	F866-109-1	3, (5-6)
268924AA	BM 07276	7731	F866-119-1	3, (5-6)
090828AB	BM 08317	7770	F850-85-2	4, (11)
269153AA	BM 08326	7800	G076-31	4, (5-8)
269154AA	BM 08335	7801	G076-27	4, (5-8)
269155AA	BM 08344	7802	G076-17	4, (5-8)
269156AA	BM 08353	7803	G076-20	4, (5-8)
269157AA	BM 08362	7804	F866-121-1	3, (5-8)
269158AA	BM 08371	7805	F866-111-3	3, (5-8)
269159AA	BM 08380	7806	F866-127-1	3, (5-8)
269160AA	BM 08399	7807	F866-123-1	3, (5-8)
269161AA	BM 08406	7808	F866-113-3	3, (5-8)
269162AA	BM 08415	7809	F866-125-1	3, (5-8)
269163AA	BM 08424	7810	F866-129-1	3, (5-8)
269164AA	BM 08433	7811	F866-89-3	3, (9)
269165AA	BM 08442	7812	G076-13	4, (9-11)
269166AA	BM 08451	7813	G076-29	4, (9-11)

TABLE 18. (Continued)

WR No.	WR Bottle No.	SoRI No.	Sample No.	Description in Quarterly Progress Report No., (pages)
002712AD	BM 11001	7838	F850-141-2	5, (13)
002712AE	BM 09565	7838	F850-141-2	5, (13)
271154AA	BM 09574	7839	F850-151-2	7, (3-5)
271155AA	BM 0	7845	G076-39-1	5, (6-8)
271156AA	BM 09592	7846	G076-43-1	5, (6-8)
271157AA	BM 09609	7847	G076-40-1	5, (6-8)
271158AA	BM 09618	7848	G076-47-1	5, (6-8)
271142AA	BM 09350	7849	G076-37-2	5, (6-8)
002250AB	BM 09369	7864	G0164-27-1	5, (12-13)
002250AC	BM 11010	7864	G0164-27-1	5, (12-13)
000156AD	BM 09378	7865	G076-54-1	5, (17-13)
271143AA	BM 09387	7866	G076-58-2	5, (12-13)
025102AU	BM 09396	7867	G076-55-2	5, (12-13)
000585AF	BM 09403	7868	G076-53-1	5, (12-13)
271144AA	BM 09412	7869	G076-59-1	5, (12-13)
000363AD	BM 09421	7870	G076-52-1	5, (12-13)
037733AC	BM 09430	7871	G076-56-1	5, (12-13)
271145AA	BM 09449	7872	G076-57-2	5, (12-13)
000351AW	BM 09458	7873	G076-51-1	7, (3-5)
271146AA	BM 09467	7908	G076-61-1	5, (9-11)
271147AA	BM 09476	7909	G076-74-1	5, (9-11)
271148AA	BM 09485	7910	G076-71-1	5, (9-11)
271149AA	BM 09494	7911	G076-75-1	5, (9-11)
000125AC	BM 09501	7913	G076-64-1	5, (9-11)
271150AA	BM 09510	7914	G076-62-1	5, (9-11)
271151AA	BM 09529	7915	G076-70-1	5, (9-11)
002852AC	BM 09538	7916	G076-78-1	5, (9-11)
271152AA	BM 09547	7917	G076-77-1	5, (9-11)
271153AA	BM 09556	7918	G076-72-1	5, (9-11)

TABLE 18. (Continued)

WR No.	WR Bottle No.	SoRI No.	Sample No.	Description in Quarterly Progress Report No., (pages)
001758AB	BM 10317	7928	G076-86-1	6, (7-9)
001757AC	BM 10326	7929	G076-89-1	6, (7-9)
272681AA	BM 10335	7930	G076-81-1	6, (7-9)
102233AB	BM 10344	7931	G076-82-1	6, (7-9)
001[illegible]8AC	BM 10353	7932	G076-87-1	6, (7-9)
2764[illegible]	BM 11029	7934	G076-107-1	6, (8)
276496A[illegible]	[illegible]11038	7984	G164-121-1	7, (3-5)
276497AA	BM [illegible]047	7985	G164-127-1	7, (3-5)
276498AA	BM 11056	7986	G0395-07-1	7, (3-5)
276499AA	BM 11065	7987	G0395-19-1	7, (3-5)
000362AB	BM 11074	8112	G076-103-1	6, (7-9)
276500AA	BM 11083	8113	G076-105-1	6, (7-9)
276501AA	BM 11092	8114	G076-109-1	6, (7-9)
002708AC	BM 11109	8115	G076-95-1	6, (7-9)
001756AB	BM 11118	8116	G076-93-1	6, (7-9)
025524AE	BM12362 or 12302	8140	G395-49-1	8, (5-8)
022032AB	BM12446	8141	G395-75-1	8, (5-8)
074813AB	BM12311	8158	G395-85-1	8, (5-8)
001055AH	BM12320	8168	G395-87-1	8, (5-8)
255378AB	BM12339	8170	G454-15-1	8, (11-12)
279194AA	BM12348	8171	G076-129-1	8, (11-12)
255375AB	BM12357	8172	G454-03-03	7, (6-8)
279150AA	BM12366	8175	G395-97-1	8, (5-8)
279151AA	BM12375	8177	G395-99-2	8, (5-8)
279152AA	BM12384	8178	G395-101-2	8, (5-8)
279153AA	BM12393	8179	G395-105-2	8, (5-8)
279154AA	BM12400	8180	G395-109-3	8, (5-8)
279155AA	BM12419	8184	G395-107-4	8, (10)
279156AA	BM12428	8190	G454-37-1	8, (11-12)

TABLE 18. (Continued)

WR No.	WR Bottle No.	SoRI No.	Sample No.	Description in Quarterly Progress Report No., (pages)
279157AA	BM12437	8191	G454-39-1	8, (11-12)
268831	BM13390	7638	F828-95-30	9, (4)
008218AR	BM14093	8197	6395-152-1	9, (2)
279299AA	BM14100	8198	H099-40-2	9, (9)
279300AA	BM14119	8211	6395-147-4	9, (9)
279301AA	BM14128	8242	H099-32-1	9, (9)
279302AA	BM14137	8243	H099-36-1	9, (9)
279303AA	BM14146	8284	H099-16-2	9, (9)
255778AB	BM14155	8354	G454-79-2	9,(8)
279306AA	BM14164	8355	G454-31-2	9, (8)
279304AA	BM14173	8356	G454-72-1	9, (8)
049410AD	BM14182	8357	G454-63-1	9, (7)
279346AA	BM14717	8362	G454-63-1	10, (5,6)
279347AA	BM14726	8563	G454-95-1	10, (7)
279348AA	BM14735	8564	G454-88-2	10, (7)
166717AB	BM14744	8565	G454-85-1	10, (6)
279349AA	BM14753	8566	G454-101-3	10, (7)
279350AA	BM14762	8567	G454-97-3	10, (6)
108236AB	BM14771	8594	H099-104-1	10, (8, 10)
279351AA	BM14780	8600	F828-103-15	10, (7)
088456AD	BM14799	8601	H270-13-30	10, (10)
009720AC	BM15796	8598	G454-82-2	11, (12)
279422AA	BM15894	8599	G454-91-2	11, (12)
279414AA	BM15803	8605	G454-119-1	11, (13)
279415AA	BM15812	8609	H270-33-27	11, (8)
279411AA	BM15750	8620	H270-49-24	11, (5)
279412AA	BM15769	8621	H270-73-15	11, (5)
028134AC	BM15778	8622	H270-77-1	11, (6)
279416AA	BM15821	8623	H270-71-20	11, (6)

TABLE 18. (Continued)

WR No.	WR Bottle No.	SoRI No.	Sample No.	Description in Quarterly Progress Report No., (pages)
279417AA	BM15830	8624	H270-59-14	11, (11)
061592AD	BM15849	8625	H099-128-1	11, (10)
217431AB	BM17085	8636	H099-142-2E	12, (4)
279472AA	BM17094	8640	H099-148-2A	12, (4)
279473AA	BM17101	8646	H445-02-A	12, (4)

TABLE 19. Candidate Compounds Tested for Anticyanide Efficacy During This Report Period (9 March, 1990 – 8 August, 1993).

ICD No.	WR No.	WR Bottle No.	SRI No.
1813	268828	BM 06019	7635
1815	268830	BM 06037	7637
1816	268831	BM 06046	7638[a]
1817	268832	BM 06055	7656
1818	268833	BM 06064	7667
1820	268835	BM 66082	7669
1822	268837	BM 06108	7671
1823	268838	BM 06117	7672
1824	268839	BM 06126	7673[a]
1825	268840	BM 06135	7674
1828	268845	BM 06199	7680
1762	268786	BM 05512	7603
1763	268787	BM 05521	7624
1764	268788	BM 05530	7625
1765	268789	BM 05549	7626
1766	268790	BM 05558	7627
1812	268827	BM 06000	7634
1814	268829	BM 06028	7636
1821	268836	BM 0609[illegible]	7670
1761	268785	BM 05503	7602
1819	268834	BM 06073	7668
1826	268841	BM 06144	7675
1827	268844	BM 06171	7678
1829	268846	BM 06206	7685
1830	268820	BM 06153	7676
1831	257838	BM 06162	7677
1832	268798	BM 06180	7679
1761	268785	BM 05503	7602

TABLE 19. (Continued)

ICD No.	WR No.	WR Bottle No.	SoRI No.
1819	268834	BM 06073	7668
1826	268841	BM 06144	7675
1830	268820	BM 06153	7676
1831	257838	BM 06162	7677
1827	268844	BM 06171	7678
1832	268798	BM 06180	7679
1829	268846	BM 06206	7685
1898	268911	BM 07141	7703
1899	268912	BM 07150	7704
1900	268913	BM 07169	7705
1901	268914	BM 07178	7720
1902	268915	BM 07187	7721
1903	268916	BM 07196	7722
1904	268917	BM 07203	7723
1905	268918	BM 07212	7724
1906	268919	BM 07221	7725
1907	268920	BM 07230	7726[a]
1908	268921	BM 07249	7727
1909	268922	BM 07258	7728
1910	268923	BM 07267	7730
1911	268924	BM 07276	7731
2008	090892	BM 08317	7730
2009	269153AA	BM 08326	7800
2012	269156AA	BM 08353	7803
2013	269157AA	BM 08362	7804
2014	269158AA	BM 08371	7805
2015	269159AA	BM 08380	7806
2016	269160+	BM 08399	7807
2019	269163AA	BM 08424	7810
2022	269166AA	BM 08451	7813

TABLE 19. (Continued)

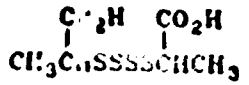
ICD No.	WR No.	WR Bottle No.	SoRI No.
2115	002712AE	BM 09565	7838
2160	271154AA	BM 09574	7839
2117	271156AA	BM 09592	7846
2118	271157AA	BM 09609	7847
2119	271158AA	BM 096180	7848
2095	000156AD	BM 09378	7865
2096	25102AV	BM 09396	7867
2097	000585AF	BM 09403	7868
2098	271144AA	BM 09912	7869
2099	000363AD	BM 09421	7870[a]
2100	037733AC	BM 09430	7871
2102	000361AW	BM 09458	7873
2104	271147AA	BM 09476	7909
2107	271148AA	BM 09485	7910
2108	271149AA	BM 09494	7911
2113	271152AA	BM 09547	7917
2114	271153AA	BM 09556	7918
2188	001758AB	BM 10317	7928
2094	271142AA	BM09350	7849
2101	271145AA	BM09449	7872
2103	271146AA	BM09467	7903
2106	002250AB	BM09369	7864
2109	000125AC	BM09501	7913[a]
2110	271150AA	BM09510	7914
2116	271155AA	BM09583	7845
2189	001757AC	BM10326	7929
2190	272681AA	BM10335	7930
2191	102233AB	BM10344	7931
2192	001868AC	BM10353	7932
2233	276495AA	BM11029	7934

TABLE 19. (Continued)

ICD No.	WR No.	WR Bottle No.	SoRI No.
2234	276496AA	BM11038	7984
2235	276497AA	BM11047	7985
2236	276498AA	BM11056	7986
2237	276499AA	BM11065	7987
2238	276500AA	BM11083	8113
2239	276501AA	BM11092	8114
2241	001756AB	BM11118	8116
2247	000362AB	BM11074	8112

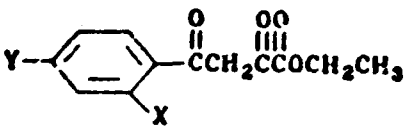
[a]Preliminary test results indicate activity.

TABLE 20. STRUCTURES OF COMPOUNDS SUBMITTED FOR TESTING AS ANTICYANIDE AGENTS.
CONTRACT NO DAMD17-90-C-0011
9 March 1990 – 8 March 1991

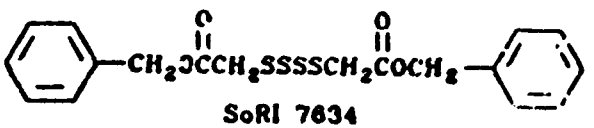


SoRI 7602

SoRI 7603

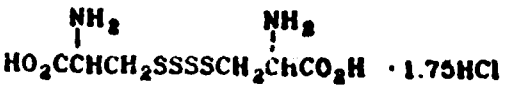


SoRI No	X	Y
7624	F	F
7625	H	H
7626	Cl	H
7627	NO_2	H



SoRI 7634

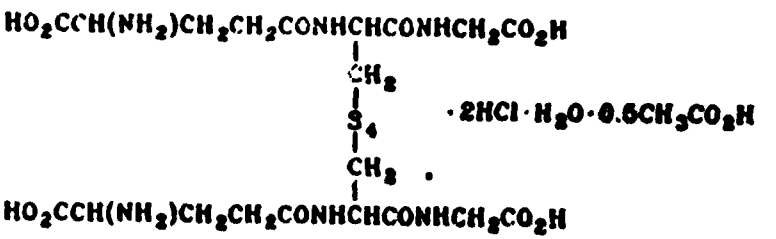
SoRI 7635



SoRI 7636

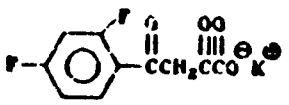
SoRI 7637 $\cdot 0.5H_2O$

SoRI 7638

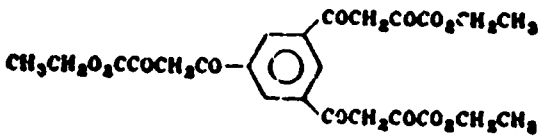


SoRI 7656

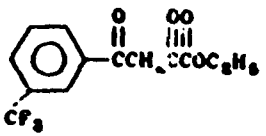
TABLE 20 (Continued)



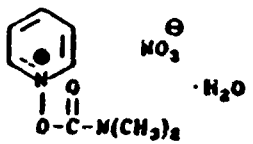
SoRI 7702



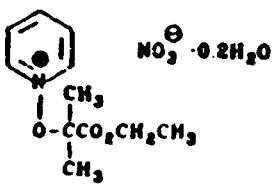
SoRI 7704



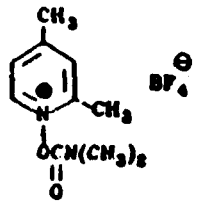
SoRI 7705



SoRI 7720

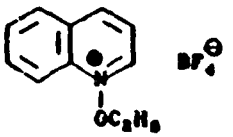


SoRI 7721

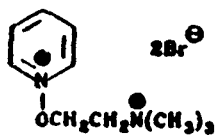


SoRI 7722

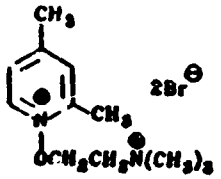
SoRI 7723



SoRI 7724



SoRI 7725



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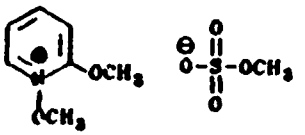
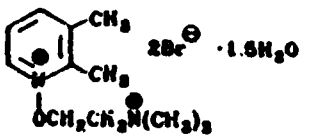


SoRI 7727



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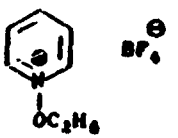
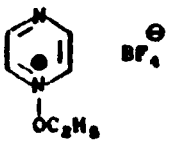
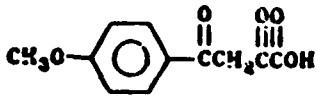


SoRI 7730

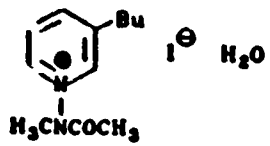


SoRI 7731

TABLE 20. (Continued)



SoRI 7770



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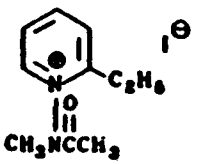
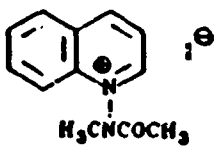
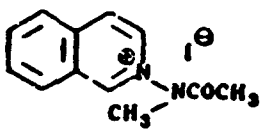


SoRI 7801



SoRI 7802



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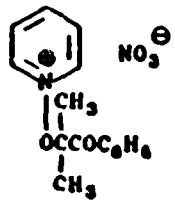
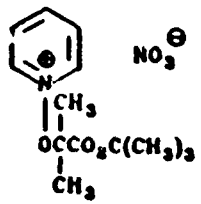


SoRI 7804



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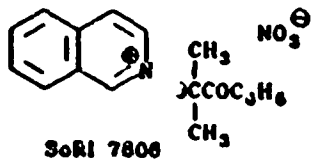

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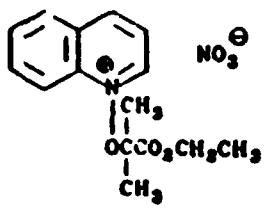

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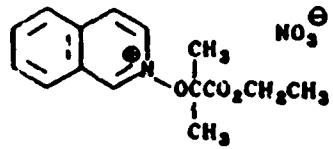

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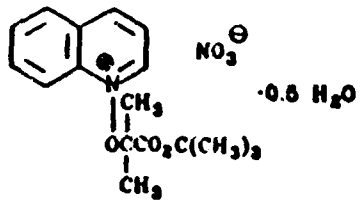
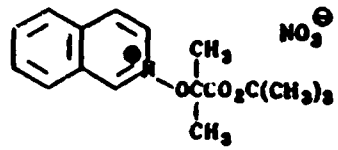
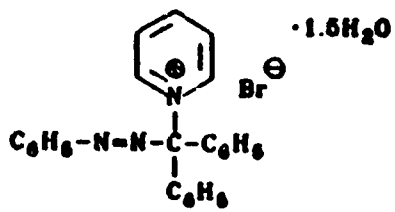


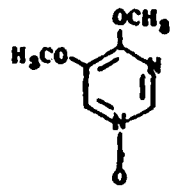
SoRI 7809



SoRI 7810



Sof 7811



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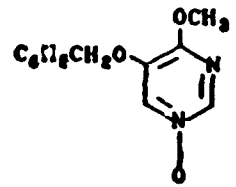
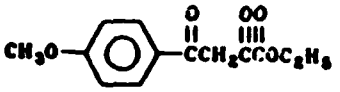
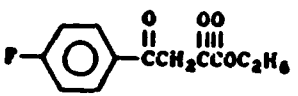


SoRI 7813

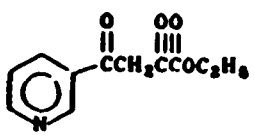
TABLE 20. (Continued)



SoRI 7667



SoRI 7668



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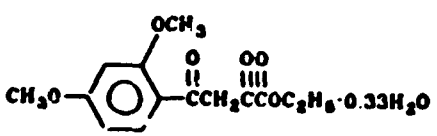

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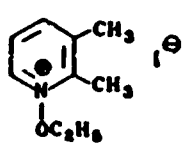
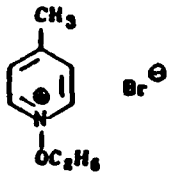
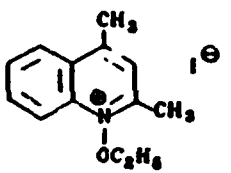


SoRI 7671



SoRI 7672

SoRI 7673



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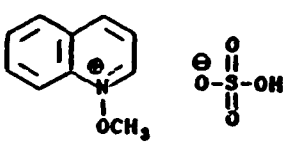

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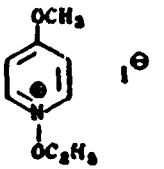

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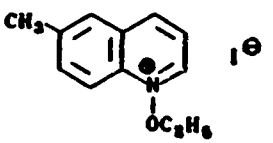

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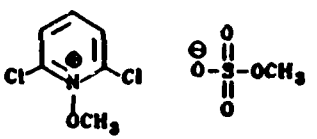

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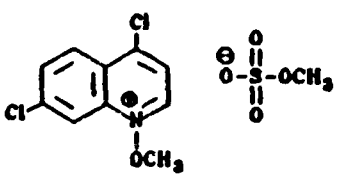

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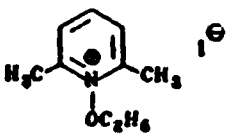

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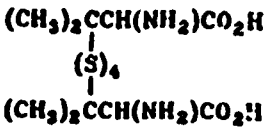
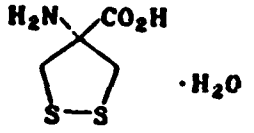
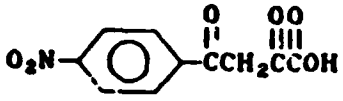
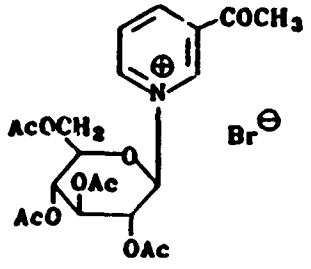


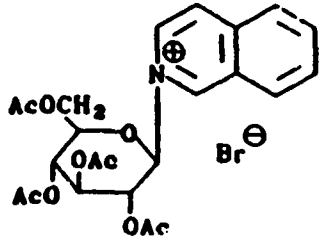
SoRI 7685

TABLE 21. STRUCTURES OF COMPOUNDS SUBMITTED FOR TESTING AS ANTICYANIDE AGENTS.
CONTRACT NO. DAMD17-90-C-0011
9 March 1991—8 March 1992


SoRI 7838


SoRI 7839


SoRI 7845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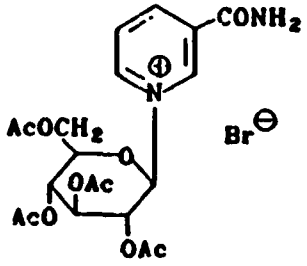
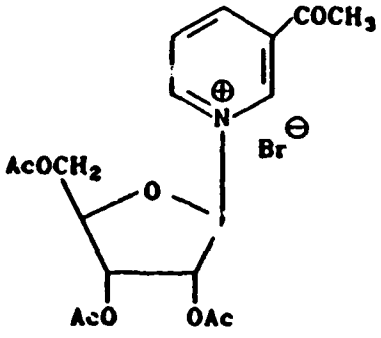
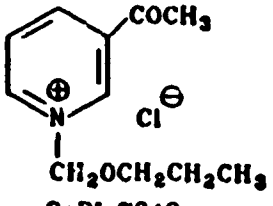

SoRI 7847


SoRI 7848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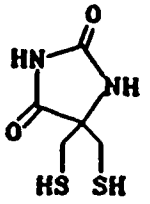
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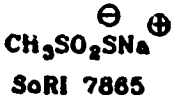
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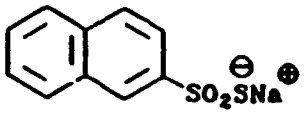
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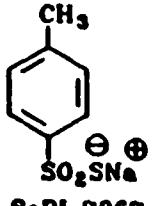
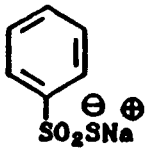
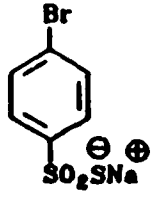

SoRI 7867


SoRI 7868


SoRI 7869

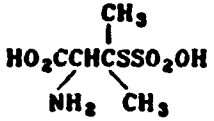
$H_2NCH_2CH_2CH_2SSO_3H$
SoRI 7870


SoRI 7871

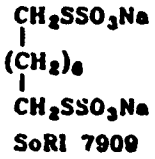

SoRI 7872

$H_2NCH_2CH_2SSO_3H$
SoRI 7873

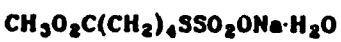
TABLE 21. (Continued)



SoRI 7908



SoRI 7909



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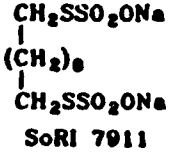

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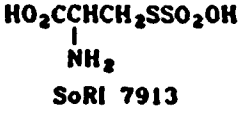

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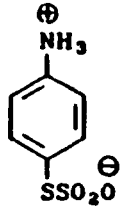
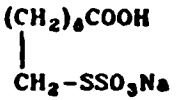
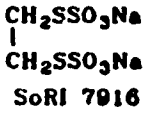


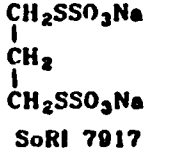
SoRI 7914



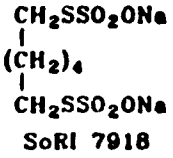
SoRI 7915



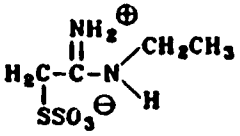
SoRI 7916



SoRI 7917



SoRI 7918



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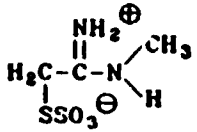

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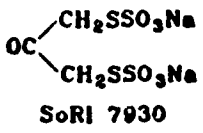

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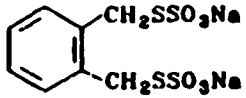

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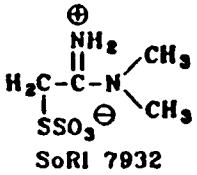
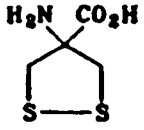
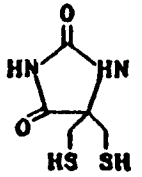


SoRI 7932

SoRI 7934



SoRI 7835



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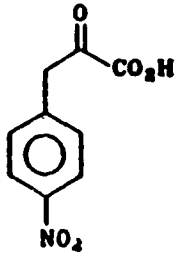
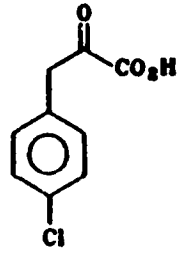
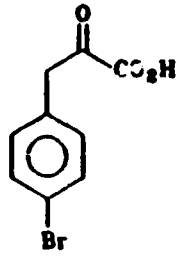


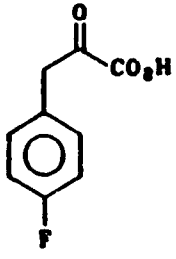
SoRI 7984



SoRI 7986

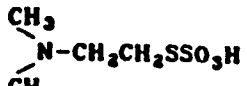


SoRI 7985

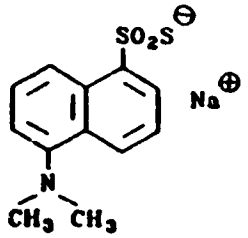


SoRI 7987

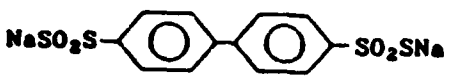
TABLE 21. (Continued)



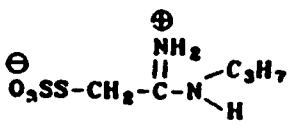
SoRI 8112



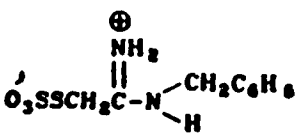
SoRI 8113



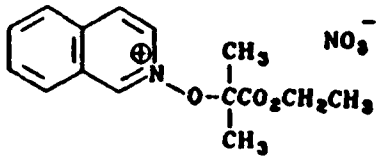
SoRI 8114



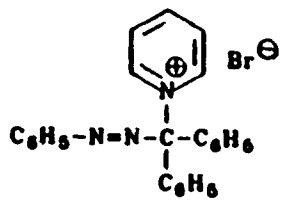
SoRI 8115



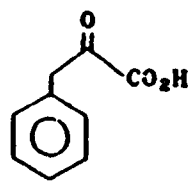
SoRI 8116



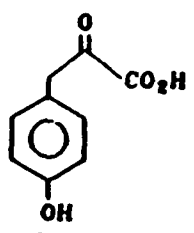
SoRI 7808



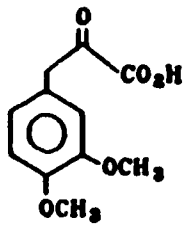
SoRI 7811



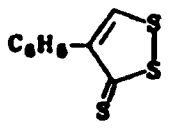
SoRI 8140



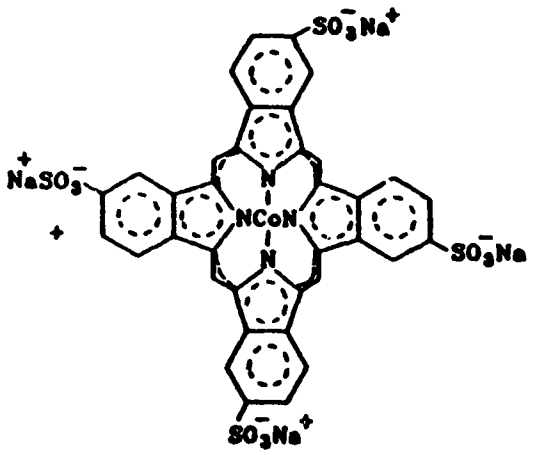
SoRI 8141



SoRI 8158

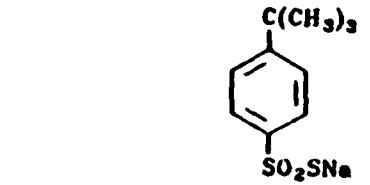


SoRI 8168

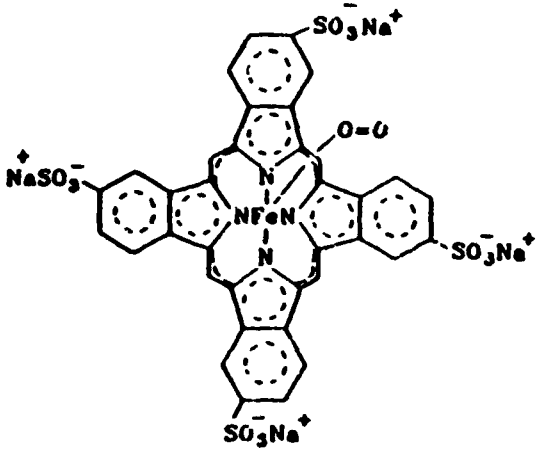


SoRI 8170

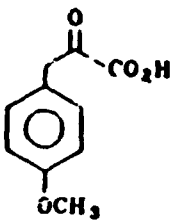
TABLE 21. (Continued)



SoRI 8171



SoRI 8172



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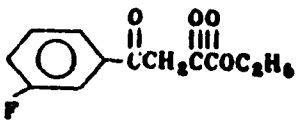
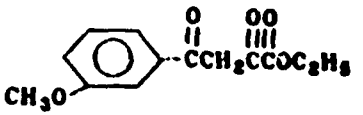
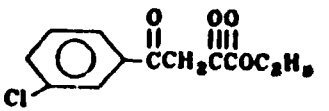


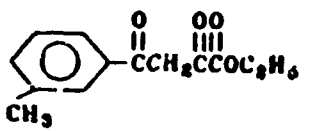
SoRI 8177



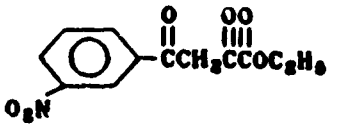
SoRI 8178



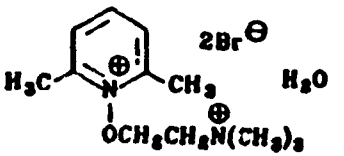
SoRI 8179



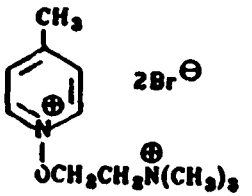
SoRI 8180



SoRI 8184



SoRI 8190

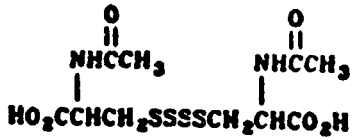


SoRI 8191

TABLE 22 STRUCTURES OF COMPOUNDS SUBMITTED FOR TESTING AS ANTICYANIDE AGENTS.

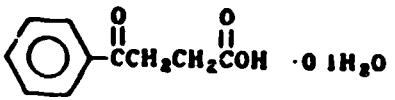
CONTRACT NO. DAMD17-90-C-0011

9 March 1992 – 19 March 1993

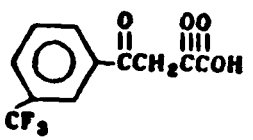


SoRI 7636

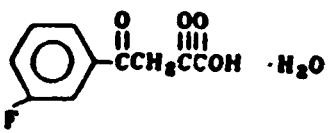
(Resynthesized at CO's request.)



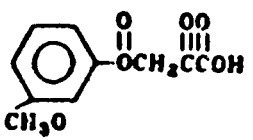
SoRI 8197



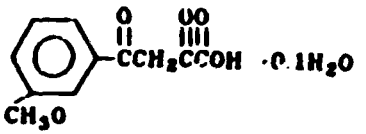
SoRI 8198



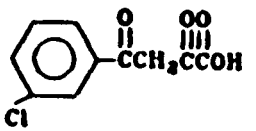
SoRI 8211



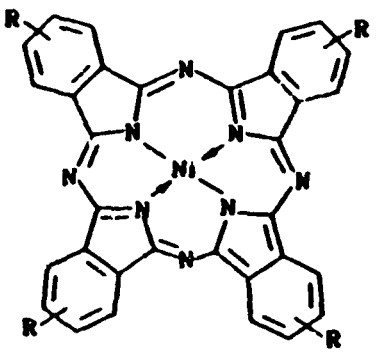
SoRI 8242



SoRI 8243

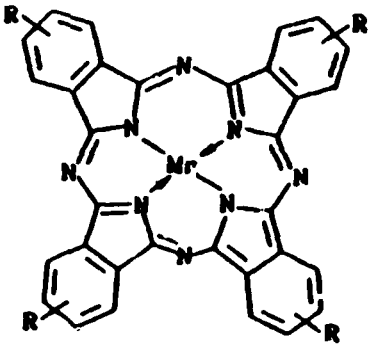


SoRI 8284



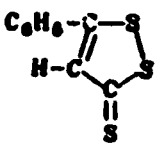
SoRI 8354

R = SO_3Na

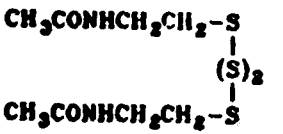


SoRI 8355

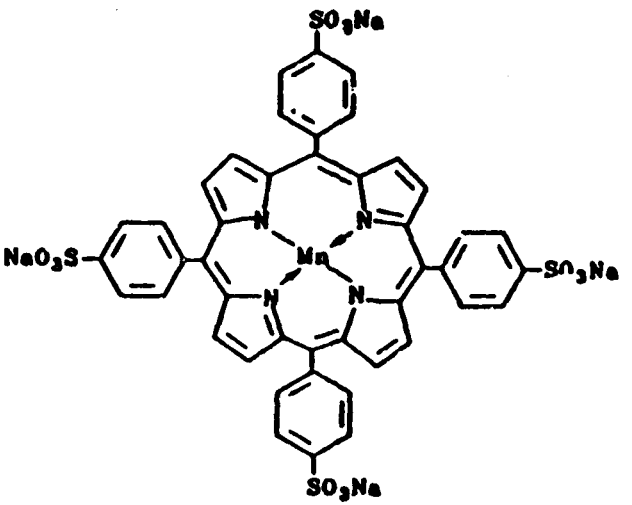
R = SO_3Na



SoRI 8357

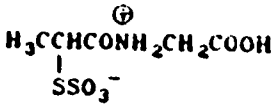


SoRI 8562



SoRI 8356

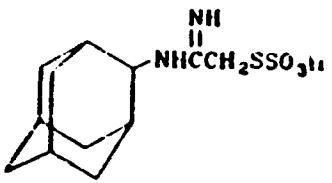
TABLE 22. (Continued)



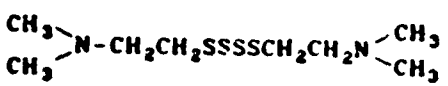
SoRI 8563

$H_2N(CH_2)_3NH(CH_2)_2SSSS(CH_2)_2NH(CH_2)_3NH_2 \cdot 4HCl$

SoRI 8564



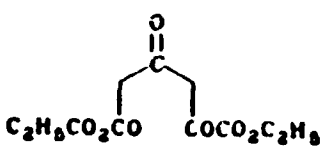
SoRI 8565



SoRI 8566

$H_2NCH_2CH_2SSSSCH_2CH_2NH_2 \cdot 2HCl$

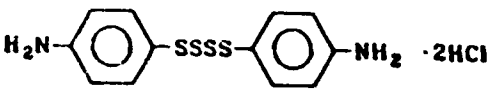
SoRI 8567



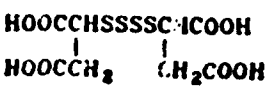
SoRI 8594

$H_2N(CH_2)_3NH(CH_2)_2SSO_3H \cdot HBr$

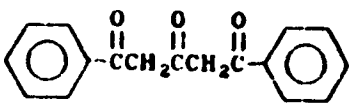
SoRI 8598



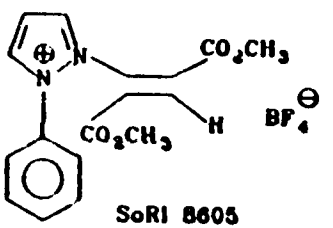
SoRI 8599



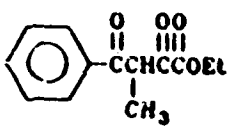
SoRI 8600



SoRI 8601



SoRI 8605



SoRI 8609

$Co_4^{+2}(NO_2)_8(NO_3)_2Co_2^{+3}(OH)_4$

SoRI 8620

$Co(NO_2)_2 \cdot 2KNO_2$

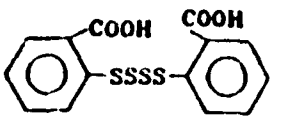
SoRI 8621

$Na_3Co(NO_2)_6$

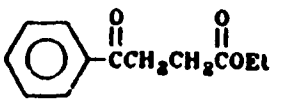
SoRI 8622

CoS_2O_3

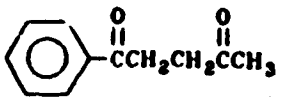
SoRI 8623



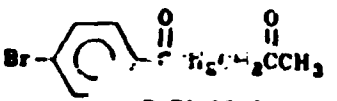
SoRI 8624



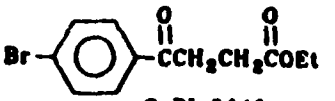
SoRI 8625



SoRI 8636



SoRI 8640



SoRI 8646